Journal of Medical Systems (2019) 43: 74
https://doi.org/10.1007/s10916-019-1173-0

SYSTEMS-LEVEL QUALITY IMPROVEMENT

Detecting Secular Trends in Clinical Treatment through Temporal Analysis

Douglas Redd[1,2] · Yijun Shao[2,3] · Yan Cheng[2,3] · Qing Zeng-Treitler[1,2]

Received: 24 March 2018 / Accepted: 21 January 2019 / Published online: 12 February 2019

Abstract
Medical treatments change over time for multiple reasons, including introduction of new treatments, availability of new scientific evidence, change in institutional guidelines, and market efforts by pharmaceutical and medical device companies. Monitoring and analyzing these secular trends will also inform the evaluation of evidence based practice as well as outcome research. Using a large national clinical dataset from the United States Veterans Health Administration (VHA), we measured the change in prevalence of all diseases, medications, and procedures by year from 2001 to 2014. To assess statistical significance, we used a generalized linear model. Among the large number of changes that were observed, multiple significant changes were related to diabetes mellitus type II (DM2). Prevalence of DM2 in the VHA increased after 2001 but plateaued by 2008; blood sugar testing by glycosylated hemoglobin increased consistently while glucose testing decreased; and the trend of insulin and metformin use was consistent with the trend in DM2 prevalence, while glyburide and rosiglitazone use dropped sharply.

Keywords Diabetes mellitus type II · Practice guidelines · Practice patterns · Data mining

Introduction

Patterns of clinical care vary over time. The ability to monitor these changes is important for assessing adherence to institutional guidelines, conformation to best treatment practices, public health surveillance, and treatment quality assessment among many other reasons. Prevalent morbidities are expected to change as treatments improve, cures are developed, and new or alternate expressions of diseases occur. For example, in one institution *C. difficile*-associated diarrhea (CDAD) was found to have increased by over four times between 1991 and 2003 [1]. Hospital admissions due to Diverticular disease increased by 26% nationwide between 1998 and 2005 [2]. Non-AIDS-defining cancers (NADC) increased by 33% in Tanzania between 2002 and 2014, while decreasing relative to all cancers [3].

In addition to these changes in disease rates, changes in treatments are also observed. An example of this is found in the use of radiotherapy in the treatment of breast cancer. Between the years of 2004–2013 the overall use of radiotherapy remained mostly stable, however the types of radiotherapy used showed substantial change. The use of hypofractionated whole-breast irradiation increased from 0.7%–15.6% for those with invasive cancer, and 0.4%–13.4% for those with ductal carcinoma in situ (DCIS). This was offset by decreased use of conventional fractionated whole-breast irradiation [4]. Also, in the treatment of Psoriatic arthritis (PsA) it has been shown that persistent use of tumor necrosis factor inhibitor (TNFi) monotherapy has decreased even though clinical trials have demonstrated its effectiveness [5].

Other changes may be due to introduction of new policies, templates, or coding systems governing the way conditions are documented, regardless of any changes in treatment patterns [6]. Recognition of these secular trends is important because some changes are clearly desirable, e.g. adoption of best practices, and some changes are clearly undesirable, e.g. increase in certain medications due to overprescription or

This article is part of the Topical Collection on *Systems-Level Quality Improvement*

✉ Qing Zeng-Treitler
zengq@gwu.edu

1 Washington DC Veterans Affairs Medical Center, 50 Irving St NW, Washington, DC 20422, USA

2 Biomedical Informatics Center, George Washington University School of Medicine and Health Sciences, 800 22nd St NW, Washington, DC 20052, USA

3 Veterans Affairs Salt Lake City Health Care System, 500 Foothill Dr, Salt Lake City, UT 84148, USA

Table 1 Summary of ICD-9, medication, and CPT prevalence values

	# Distinct Values	Max Prev.	Min Prev.	Mean Prev.	Median Prev.
ICD-9	14,688	0.48	0	0.00081	8.7^{-6}
Medication	2589	0.28	0	0.00289	2.0^{-5}
Procedure	16,381	0.85	0	0.00114	2.6^{-6}

decrease in certain medications due pharmaceutical companies' advertisement effort of non-generic alternatives. Monitoring these changes closely will enable the promotion and facilitation of positive changes as well as the early detection of negative ones.

Before embarking on fully automated monitoring programs, it is important to evaluate the type and extent of changes, and attempt to identify the cause. We analyzed the electronic medical records of patients from the U.S. Veterans Health Administration (VHA) for temporal changes in diagnoses, procedures, and medications between the years of 2001 and 2014 to identify significant changes in documented clinical treatment over time.

Methods

All data used in this study was accessed through the VA Informatics and Computing Infrastructure (VINCI) program of the VHA in accordance with IRB approval [7]. This data resource includes medical records of over 20 million patients, over 1 billion principal diagnosis ICD codes, over 3.5 billion procedure codes (CPT and ICD), and over 1 billion prescriptions from 152 medical centers.

The data was aggregated from the individual VistA electronic medical record systems at the VHA medical centers across the United States. Data was used from diagnosis, procedure, and prescription data domains. The VHA transitioned from ICD-9 to ICD-10 disease billing codes in fiscal year 2016, which began on Oct. 1, 2015. To account for this, we restricted our data to include entries through the end of the calendar year 2014. We did this in order to avoid variance introduced by the coding transition.

Diagnoses were measured by ICD-9-CM code, procedures by CPT code, and medications by standardized drug name in prescription records. All data was aggregated by patient and year. Total patient counts were collected by year and used to determine prevalence.

Prevalence was calculated for diseases, procedures, and medications for each patient and year. In order to determine

Table 2 ICD-9 codes with the 20 highest standard deviations in crude prevalence. Direction of change is indicated by + (increasing), − (decreasing) or ¿ (indeterminate)

ICD-9	Description	St. Dev. (p value)	+−
V04.81	Need for prophylactic vaccination and inoculation against influenza	0.106 (0.0075)	+
V04.8	Need for prophylactic vaccination and inoculation against other viral diseases	0.080 (0.0097)	−
272.4	Other and unspecified hyperlipidemia	0.058 (0.0001)	+
V65.40	Counseling NOS	0.052 (<.0001)	+
V65.49	Other specified counseling	0.040 (0.0002)	+
600.0	Hyperplasia of prostate	0.038 (0.0042)	−
V65.9	Unspecified reason for consultation	0.037 (0.0041)	+
600.00	Hypertrophy (benign) of prostate without urinary obstruction and other lower urinary tract symptom (LUTS)	0.035 (0.0041)	+
V58.83	Encounter for therapeutic drug monitoring	0.032 (<.0001)	+
401.9	Unspecified essential hypertension	0.030 (0.3144)	¿
V79.1	Screening for alcoholism	0.029 (<.0001)	−
309.81	Posttraumatic stress disorder	0.027 (<.0001)	+
724.2	Lumbago	0.027 (<.0001)	+
414.00	Coronary atherosclerosis of unspecified type of vessel, native or graft	0.025 (<.0001)	−
V72.6	Laboratory examination	0.024 (0.0042)	−
V68.01	Disability examination	0.023 (<.0001)	+
V72.2	Dental examination	0.023 (0.6522)	¿
V389.18	Sensorineural hearing loss, bilateral	0.022 (<.0001)	+
V268.9	Unspecified vitamin D deficiency	0.021 (<.0001)	+
V79.0	Screening for depression	0.021 (<.0001)	−

which values changed the most over time, we calculated the standard deviation (SD) of the yearly prevalence values. Those prevalence values with the highest significant SDs were then analyzed in more detail, interrogating their patterns of change by year.

The univariate trend analysis for each individual disease, procedure, and medication was conducted via simple general linear model (GLM) with prevalence as the dependent variable and year as the independent variable. The range of year was so small relative to its mean that there may be loss of accuracy in the computations, so we rescaled and standardized year into a variable with mean of 0 and SD of 1. The trend direction was determined according to the sign of coefficient estimate with positive indicating increasing and negative indicating decreasing. Since patient age and disease structure by year would potentially influence the trend, multiple GLM was also conducted with age and disease adjusted. The correlation between disease and treatment was estimated using Pearson Correlation coefficient.

To avoid familywise errors caused by multiple testing, we applied the Bonferonni Correction [8] method to set a more restrictive alpha level than the traditional level of 0.05. We had a total of 330 tests in this study, with 100 each for diagnosis, medication, and procedure prevalence, 14 tests for DM2-related prevalence, and 16 tests for correlation between DM2 and medications. According to the Bonferonni Correction, we set the alpha level = 0.05/330 = 0.000152. This indicates that a test with p value equal to or less than 0.0001 suggests statistical significance.

Results

Since the prevalence of each procedure, ICD-9 code, and medication was observed for 14 years from 2001 to 2014, the average of prevalence for each procedure, ICD-9 code, and medication was used as an estimate for the overall prevalence.

A total of 16,381 procedures, 14,688 ICD-9 codes, and 2589 medications were found (Table 1). In each case, there was a long tail of many entities with very small prevalence values, with minimum values small enough that precision was lost. The ICD-9 code with the highest variance in prevalence was V04.81, influenza vaccination (Table 2). Omeprazole was the medication with the highest variance in prevalence, 0.090 (Table 3). The procedure with the highest variance in prevalence was HC PRO PHONE CALL 5–10 MIN, at 0.228 (Table 4).

In further analysis, we focused on DM2-related changes because examination of the variables with the highest significant

Table 3 Medications with the 20 highest standard deviations in crude prevalence

Medication	St. Dev. (p value)	+–
Omeprazole	0.090 (0.0101)	+
Simvastatin	0.062 (0.1542)	¿
Rabeprazole	0.060 (0.0033)	–
Amlodipine	0.055 (<.0001)	+
Vardenafil	0.047 (0.4032)	¿
Felodipine	0.044 (0.0002)	–
Sildenafil	0.041 (0.2439)	¿
Atorvastatin	0.040 (0.0210)	+
Cholecalciferol	0.033 (<.0001)	+
Acetaminophen/Hydrocodone	0.032 (<.0001)	+
Ranitidine	0.030 (<.0001)	–
Aspirin	0.028 (0.0214)	–
Albuterol	0.027 (<.0001)	+
Fosinopril	0.026 (<.0001)	–
Rosuvastatin	0.026 (0.0011)	+
Atenolol	0.025 (<.0001)	–
Lisinopril	0.025 (<.0827)	¿
Loratadine	0.024 (0.2463)	¿
Tramadol	0.023 (<.0001)	+
Lansoprazole	0.022 (0.0230)	–

Direction of change is indicated by + (increasing), − (decreasing) or ¿ (indeterminate)

Table 4 Procedures with the 20 highest standard deviations in crude prevalence

Procedure	St. Dev. (p value)	+–
HC PRO PHONE CALL 5–10 MIN	0.228 (<.0001)	+
PHYSICIAN PHONE CONSULTATION	0.200 (0.0003)	–
SUPPLY/ACCESSORY/SERVICE	0.110 (0.3184)	¿
HC PRO PHONE CALL 11–20 MIN	0.092 (<.0001)	+
GLYCOSYLATED HEMOGLOBIN TEST	0.091 (<.0001)	+
COMPREHEN METABOLIC PANEL	0.089 (<.0001)	+
LIPID PANEL	0.084 (<.0001)	+
COMPLETE CBC W/AUTO DIFF WBC	0.078 (0.0003)	+
FLU VACCINE 3 YRS & > IM	0.076 (0.5289)	¿
ASSAY THYROID STIM HORMONE	0.073 (<.0001)	+
FLU VACCINE NO PRESERV 3 & >	0.070 (<.0001)	+
PHONE E/M PHYS/QHP 5–10 MIN	0.065 (<.0001)	+
OCCULT BLOOD FECES	0.060 (<.0001)	–
VITAMIN D 25 HYDROXY	0.058 (<.0001)	+
IMMUNIZATION ADMIN	0.058 (<.0001)	+
URINALYSIS AUTO W/O SCOPE	0.058 (<.0001)	+
ASSAY OF URINE CREATININE	0.046 (<.0001)	+
MICROALBUMIN QUANTITATIVE	0.045 (<.0001)	+
VITAMIN B-12	0.044 (<.0001)	+
HC PRO PHONE CALL 21–30 MIN	0.044 (<.0001)	+

Direction of change is indicated by + (increasing), − (decreasing) or ¿ (indeterminate)

Table 5 Direction of change and standard deviation (p value) for entities with significant change

Entity	Crude Analysis				Adjusted Analysis		
	+−	Absolute Coefficient	St. Dev. Of Prevalence	p value	+−	Absolute Coefficient	p value
Disease							
Diabetes Mellitus Type 2 (ICD-9-CM 250.00)	+	0.0146	0.0167	<.0001	+	0.0196	<.0001
Medications							
Insulin	+	0.0102	0.0108	<.0001	+	0.0078	<.0001
Rosiglitazone	–	0.0076	0.0111	0.0048	–	0.0173	0.0028
Glyburide	–	0.0182	0.0193	<.0001	–	0.0273	<.0001
Metformin	+	0.0116	0.0130	<.0001	¿	0.0015	0.1213
Tests							
Glucose Test	–	0.0122	0.0134	<.0001	–	0.0122	<.0001
Glycosylated Hemoglobin Test (A1C)	+	0.0889	0.0919	<.0001	+	0.0726	<.0001

Direction of change is indicated by + (increasing), − (decreasing) or ¿ (indeterminate). Direction of change and adjusted *p* values are shown, with disease and tests adjusted for age, and medications adjusted for primary indication

SD revealed that multiple DM2 related treatments displayed significant deviation during the time period analyzed (Table 5). The ICD-9 code of 250.00 (ranked 32) showed increasing prevalence, with a SD of 0.0167, *p* value <0.0001 (Table 5 and Fig. 1). The DM2 medications rosiglitazone (brand name Avandia) and glyburide (brand names Micronase, DiaBeta, and Glynase) had decreasing prevalence values (SDs of 0.0111, *p* value 0.0048, and 0.0193, p value <.0001), while insulin and metformin showed an increasing prevalence (SDs of 0.0108, p value <.0001, and 0.0130, p value <.0001) (Table 5 and Fig. 2). The traditional glucose test had a decreasing prevalence (SD 0.0134, p value <.0001), while the newer Glycosylated Hemoglobin Test (A1C) had an increasing prevalence (SD 0.0919, p value <.0001) (Table 5 and Fig. 3).

DM2 showed significant positive correlation with insulin and metformin, and negative correlation with glyburide. Correlation with rosiglitazone was moderately negative but not significant (Table 6). When stratifying by age group, the pattern stayed the same except for the 18–35 age group. Besides insulin, this age group was almost the inverse of the others with rosiglitazone and glyburide having a significant positive correlation with DM2, and metformin a moderately negative correlation (Table 7, 8 and 9).

Other commonly used DM2 medications did not have as high of change in prevalence. There were many combinations of metformin that had relatively high prevalence values, but did not have as high of levels of change in prevalence. Metformin alone had a SD of 0.0130 and glyburide/

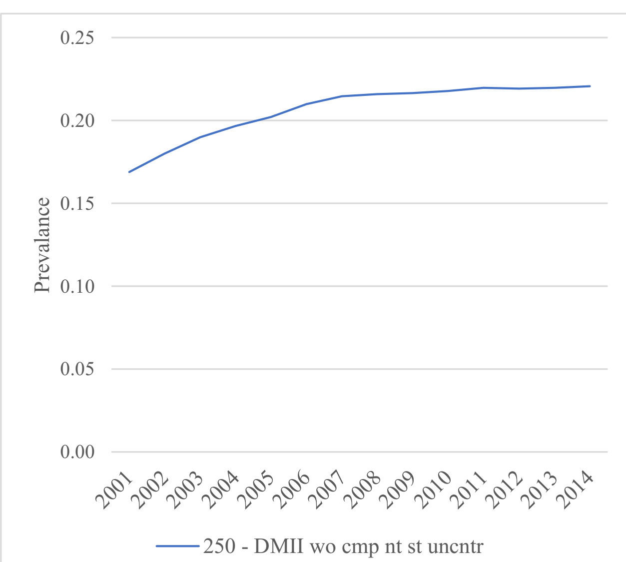

Fig. 1 Secular trend in crude prevalence of diabetes mellitus type 2 (ICD-9-CM code 250.00) in the VHA nationwide electronic health records

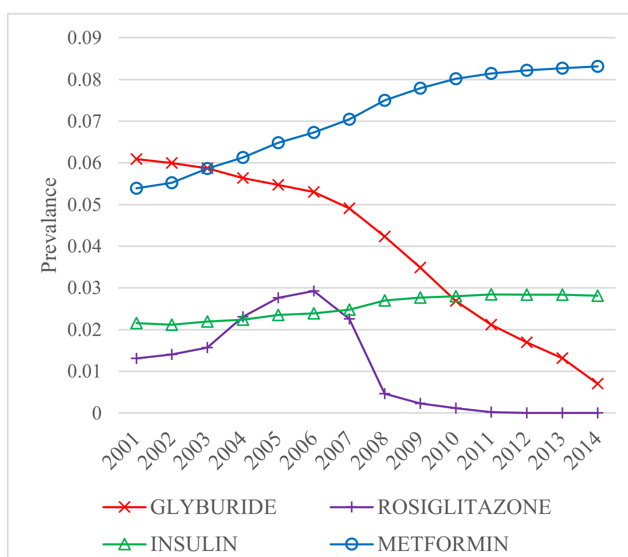

Fig. 2 Secular trend in crude prevalence of diabetes mellitus type 2 medications with significant changes in prevalence

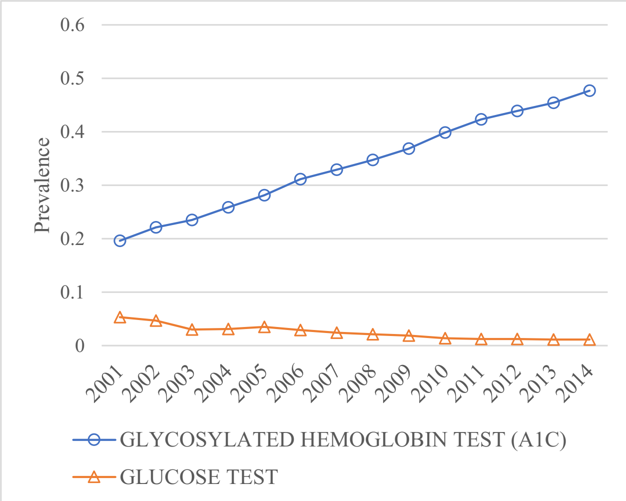

Fig. 3 Diabetes Mellitus Type 2 tests with significant changes in crude prevalence

metformin (brand name Glucovance) a SD of 0.0058. Other metformin combinations had much lower SDs. Pioglitazone (brand name Actos) has a SD of 0.0027, and its combination with metformin has an SD of nearly zero.

Discussion

The ability to monitor patterns of medical practice over time is important for many reasons: monitoring of conforming to best treatment practices, institutional guidelines, public health surveillance, and treatment quality indication being just a few. We have demonstrated the ability to discover significant changes in treatment patterns over time for diabetes mellitus type II (DM2). The observed changes confirm some expectations, but also reveal some interesting variances.

The prevalence of insulin and metformin use increased, however use of two other DM2 medications, glyburide and rosiglitazone, decreased. Glyburide carries a risk of hypoglycemia, particularly in the elderly [9]. With the aging population of the VA, doctors may be showing preference for other suitable medications.

Rosiglitazone prevalence dropped to 0 in 2012. This is likely due to evidence of increasing cardiovascular events and death, resulting in additional restrictions by the U.S. Food and Drug Administration (FDA) in November 2011 [10]. Although the restrictions were lifted in 2013, it is still not used in this population. Additionally, there have been an increase in the number of alternative DM2 drugs [11]. Other DM2 drugs did not show as high of change in prevalence, and are more stable in their pattern of usage.

Table 6 Pearson Correlation between DM2 and Medications

	Correlation Coefficient	P Value
DM2 / Insulin	0.94	<.0001
DM2 / Rosiglitazone	−0.46	0.0961
DM2 / Glyburide	−0.79	0.0009
DM2 / Metformin	0.99	<.0001

Table 7 Pearson Correlation between DM2 and Medications among Age Group 18–35

	Correlation Coefficient	*P* Value
DM2 / Insulin	0.96	<.0001
DM2 / Rosiglitazone	0.64	0.0451
DM2 / Glyburide	0.88	<.0001
DM2 / Metformin	−0.58	0.0298

Overall, insulin and metformin showed strong positive correlation with DM2, and glyburide and rosiglitazone a more moderate negative correlation. Interestingly, in the 18–35 age group glyburide and rosiglitazone show a positive correlation, and metformin a negative correlation. This may be a side effect of glyburide and rosiglitazone showing increased risk for hypoglycemia, which is primarily of concern in the elderly. Since the 18–35 year old group does not have this increased risk there may be a preference for these medications [9, 12]. Further investigation of this difference in medication for the 18–35 age group would be informative.

There were significant changes in the prevalence of two DM2 related laboratory tests, with the prevalence of the glycosylated hemoglobin test increasing and that of the glucose test decreasing. The glycosylated hemoglobin test measures the plasma glucose concentration average over the previous 3 months [13]. In contrast, the glucose test measures blood glucose levels at a single point in time. This likely explains the increasing preference for the glycosylated hemoglobin test due to its better overall indication of blood sugar levels.

By discovering changes in treatment practices, overall delivery of health services can be improved. Conformance to guidelines can be confirmed as well as detection of significant disease rate and treatment pattern changes. New policies can be created to address negative patterns, and investigation of positive patterns can lead to dissemination of successful treatments. Many patterns are incomplete however, and further investigation is

Table 8 Pearson Correlation between DM2 and Medications among Age Group 36–50

	Correlation Coefficient	*P* Value
DM2 / Insulin	0.90	<.0001
DM2 / Rosiglitazone	−0.30	0.3748
DM2 / Glyburide	−0.80	0.0006
DM2 / Metformin	0.96	<.0001

Table 9 Pearson Correlation between DM2 and Medications among Age Group 51–65

	Correlation Coefficient	P Value
DM2 / Insulin	0.97	<.0001
DM2 / Rosiglitazone	−0.46	0.0943
DM2 / Glyburide	−0.69	0.0062
DM2 / Metformin	0.99	<.0001

required in order to confirm causes of the patterns observed. Changes due to modification of coding rules need to be distinguished from real changes in disease prevalence. Information extraction needs to account for changing documentation patterns in order to maintain accuracy. Tools based on natural language processing need to be adapted to new language patterns and sublanguages in progress notes [14–17].

We only examined the diseases, medications, and procedures that fell within the top 100, ranked by standard deviation, which limits the strength of specific conclusions about DM2 in this population. The only DM2 ICD-9-CM code in the top 100 was 250.00, however there are many more specific DM2 codes indicating ketoacidosis, hyperosmolarity, coma, renal, ophthalmic, neurological manifestations, etc. Future work needs to analyze the use of additional disease codes, medications, and tests to obtain a more complete picture. Those discussed here had the highest changes in usage, however the cumulative effect of other changes would also be informative.

Conclusions

Discovery of changing medical practice patterns is important for measuring the quality of health care being delivered, conformance to institutional guidelines, and revealing anomalies that merit further investigation. We find a possible plateau in diabetes mellitus type II prevalence in this population that may indicate successful interventions. We find a large decrease in the use of rosiglitazone, which may be unwarranted now that the FDA has reversed its restrictions due to new evidence. We also observe the increased use of glycosylated hemoglobin testing along with a decrease in glucose testing, indicating clinician preference.

Funding This study was funded by

• HIR 08–374 VA Health Services Research and Development Consortium for Healthcare Informatics Research (CHIR)

• HIR 08–204 Veterans Affairs Health Services Research & Development, VA Informatics and Computing Infrastructure (VINCI) aka Center for Scientific Computing

• CRE 12–315 Veterans Affairs Health Services Research & Development, CREATE: A VHA NLP Software Ecosystem for Collaborative Development and Integration

• UL1TR001876 and KL2TR001877 NIH National Center for Advancing Translational Sciences, Clinical and Translational Science Institute at Children's National (CTSI-CN), National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA)

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Pepin, J., Valiquette, L., Alary, M. E., Villemure, P., Pelletier, A., Forget, K., Pepin, K., and Chouinard, D., Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne. 171(5):466–472, 2004. https://doi.org/10.1503/cmaj.1041104.
2. Etzioni, D. A., Mack, T. M., Beart, Jr., R. W., and Kaiser, A. M., Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann. Surg. 249(2):210–217, 2009. https://doi.org/10.1097/SLA.0b013e3181952888.
3. Campbell, J. A., Soliman, A. S., Kahesa, C., Harlow, S. D., and Msemo, D., Changing Patterns of lung, liver, and head and neck non-AIDS-defining cancers relative to HIV status in Tanzania between 2002-2014. Infect Agent Cancer. 11:58, 2016. https://doi.org/10.1186/s13027-016-0106-5.
4. Hasan, Y., Waller, J., Yao, K., Chmura, S. J., and Huo, D., Utilization trend and regimens of hypofractionated whole breast radiation therapy in the United States. Breast Cancer Res. Treat. 162(2):317–328, 2017. https://doi.org/10.1007/s10549-017-4120-0.
5. Mease, P. J., Lesperance, T., Liu, M., Collier, D. H., Mason, M., Deveikis, S., and Accortt, N. A., Changes in Treatment Patterns in Patients with Psoriatic Arthritis Initiating Biologic and Nonbiologic Therapy in a Clinical Registry. J. Rheumatol. 44(2):184–192, 2017. https://doi.org/10.3899/jrheum.160343.
6. Topaz, M., Shafran-Topaz, L., and Bowles, K. H., ICD-9 to ICD-10: evolution, revolution, and current debates in the United States. Perspect Health Inf Manag. 1d:10, 2013.
7. Yang, X., Soohoo, M., Streja, E., Rivara, M. B., Obi, Y., Adams, S. V., Kalantar-Zadeh, K., and Mehrotra, R., Serum Magnesium Levels and Hospitalization and Mortality in Incident Peritoneal Dialysis Patients: A Cohort Study. Am. J. Kidney Dis. 68(4):619–627, 2016. https://doi.org/10.1053/j.ajkd.2016.03.428.
8. Bonferroni, CE. Teoria statistica delle classi e calcolo delle probabilità. Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commerciali di Firenze, 1936.
9. Chiniwala, N., and Jabbour, S., Management of diabetes mellitus in the elderly. Curr Opin Endocrinol Diabetes Obes. 18(2):148–152, 2011. https://doi.org/10.1097/MED.0b013e3283444ba0.
10. Loke, Y. K., Kwok, C. S., and Singh, S., Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 342:d1309, 2011. https://doi.org/10.1136/bmj.d1309.
11. Olokoba, A. B., Obateru, O. A., and Olokoba, L. B., Type 2 diabetes mellitus: a review of current trends. Oman Med J. 27(4):269–273, 2012. https://doi.org/10.5001/omj.2012.68.
12. Lee, S. J., Boscardin, W. J., Stijacic Cenzer, I., Huang, E. S., Rice-Trumble, K., and Eng, C., The risks and benefits of implementing glycemic control guidelines in frail older adults with diabetes

mellitus. J. Am. Geriatr. Soc. 59(4):666–672, 2011. https://doi.org/10.1111/j.1532-5415.2011.03362.x.

13. Miedema, K., Standardization of HbA1c and Optimal Range of Monitoring. Scand. J. Clin. Lab. Investig. Suppl. 240:61–72, 2005. https://doi.org/10.1080/00365510500236143.
14. Doing-Harris, K., Patterson, O., Igo, S., and Hurdle, J., Document sublanguage clustering to detect medical specialty in cross-institutional clinical texts. San Francisco. 2512101: ACM: Proceedings of the 7th international workshop on Data and text mining in biomedical informatics, 2013, 9–12.
15. Friedman, C., Kra, P., and Rzhetsky, A., Two biomedical sublanguages: a description based on the theories of Zellig Harris. J. Biomed. Inform. 35:222–235, 2002. https://doi.org/10.1016/S1532-0464(03)00012-1.
16. Patterson, O., and Hurdle, J. F., Document clustering of clinical narratives: a systematic study of clinical sublanguages. AMIA Annual Symposium proceedings / AMIA Symposium AMIA Symposium. 2011:1099–1107, 2011.
17. Zeng, Q. T., Redd, D., Divita, G., Jarad, S., Brandt, C., and Nebeker, J. R., Characterizing Clinical Text and Sublanguage: A Case Study of the VA Clinical Notes. J Health Med Informat. 4(2), 2011. https://doi.org/10.4172/2157-7420.S3-001.