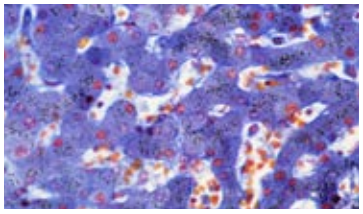
research

A quarter of outpatient antibiotic prescriptions are inappropriate finds classification scheme p 101

Financial interests are prevalent among patient organisations involved in NICE appraisals p 102



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ORIGINAL RESEARCH ICD-10-CM based cross sectional study

Appropriateness of outpatient antibiotic prescribing among privately insured US patients

Chua K-P, Fischer MA, Linder JA

Cite this as: *BMJ* 2019;364:k5092
Find this at: http://dx.doi.org/10.1136/bmj.k5092

Study question Among privately insured US children and non-elderly adults in 2016, what proportion of outpatient antibiotic prescriptions were for appropriate indications?

Methods This cross sectional study analysed data from the 2016 MarketScan Commercial Claims and Encounters database, which includes claims from non-elderly enrollees who receive private health insurance from their employer. The cohort comprised 19.2 million enrollees aged 0-64 years. The authors developed a classification scheme determining whether each of the 91 738 ICD-10-CM (international classification of diseases-clinical modification, 10th revision) diagnosis codes "always," "sometimes," or "never" justified antibiotics. For each antibiotic prescription filled by the cohort, this scheme was used to classify all diagnosis codes in claims occurring on the day of fills and during the three days before fills. Based on the classification of these codes, the fills were assigned to one of four mutually exclusive categories: appropriate, potentially appropriate, inappropriate, and not associated with a recent diagnosis code. The main outcome was the proportion of fills in each category.

Study answer and limitations Among 15 455 834 outpatient antibiotic prescriptions filled by the cohort, 1 973 873 (12.8%) were appropriate, 5 487 003 (35.5%) were potentially appropriate, 3 592 183 (23.2%) were inappropriate, and 4 402 775 (28.5%) were not associated with a recent diagnosis code. Limitations include reliance on diagnosis codes, use of a classification scheme based on consensus, and uncertain generalisability.

What this study adds According to a novel classification scheme of 91 738 ICD-10-CM diagnosis codes, almost a quarter of outpatient antibiotic prescription fills by a cohort of 19 million non-elderly people in 2016 were inappropriate, while more than a third were only potentially appropriate. The classification scheme could facilitate efforts to comprehensively measure outpatient antibiotic appropriateness in the US and could be adapted for use in other countries that use ICD-10 codes.

Funding, competing interests, and data sharing This study was funded by the Agency for Healthcare Research and Quality. No competing interests. Programming code available on request.

Proportion of antibiotic prescription fills in each appropriateness category, and proportion of cohort filling at least one prescription in each category, MarketScan 2016

	Proportion of fills in each category (%)*			Proportion of cohort filling ≥1 antibiotic prescription in each category in 2016 (%)†		
Categories	Overall (n=15 455 834 fills)	Adults (n=11 780 881 fills)	Children (n=3 674 953 fills)	Overall (n=19 203 264 enrollees)	Adults (n=14 571 944 enrollees)	Children (n=4 631 320 enrollees)
Appropriate	1 973 873 (12.8)	1 347 569 (11.4)	626 304 (17.0)	1 446 673 (7.5)	973 292 (6.7)	473 381 (10.2)
Potentially appropriate	5 487 003 (35.5)	3 696 473 (31.4)	1 790 530 (48.7)	3 750 225 (19.5)	2 610 416 (17.9)	1 139 839 (24.6)
Inappropriate	3 592 183 (23.2)	2 965 194 (25.2)	626 989 (17.1)	2 697 918 (14.1)	2 207 173 (15.2)	490 745 (10.6)
Not associated with recent diagnosis code	4 402 775 (28.5)	3 771 645 (32.0)	631 130 (17.2)	2 756 082 (14.4)	2 360 472 (16.2)	395 610 (8.5)

*Proportions are mutually exclusive.
†Proportions are not mutually exclusive.

Patient organisations, NICE, and conflict of interest

ORIGINAL RESEARCH Policy review

Financial interests of patient organisations contributing to health technology assessment at England's National Institute for Health and Care Excellence

Mandeville KL, Barker R, Packham A, Sowerby C, Yarrow K, Patrick H

Cite this as: *BMJ* 2019;364:k5300
Find this at http://dx.doi.org/10.1136/bmj.k5300

Study question What is the prevalence of financial interests among patient organisations contributing to health technology assessment at the National Institute for Health and Care Excellence (NICE) in England and the extent to which NICE's disclosure policy makes decision making committees aware of these interests?

Methods This study assessed 53 patient organisations contributing to 41 technology appraisals in 2015 and 2016, with 117 separate occasions that an organisation contributed to a technology appraisal. Pharmaceutical industry funding was determined from manufacturers' declarations and accounts, annual reports, websites, and responses from patient organisations. Evidence of specific interests (funding from the manufacturer(s) of a technology or a competitor product in the same year that a patient organisation had contributed to the appraisal of that technology or the previous year) was compared with declarations of interests by nominated representatives of patient organisations.

Study answer and limitations 38/53 (72%) patient organisations held specific interests. Specific interests were present on 92/117 (79%) occasions that patient organisations contributed to appraisals. NICE's committees were aware of less than a quarter (30/144; 21%) of specific interests. For almost two thirds (71/114; 62%) of specific interests not known to committees, disclosure by patient organisations was not required by NICE's policy. The study was limited by incomplete and inconsistent reporting by patient organisations and manufacturers.

What this study adds Specific interests are highly prevalent among patient organisations contributing to technology appraisals at NICE. Such interests need to be systematically identified to improve transparency.

Competing interests, funding, and data sharing HP is an employee of NICE. KLM did a specialty training placement at NICE before starting this work. No specific funding was received for this study. A dataset of publicly available data used in the study is available from kate.mandeville@lshtm.ac.uk.

COMMENTARY Voluntary disclosure isn't working

As non-profit public charities, patient organisations seek to combat particular diseases or disabilities by increasing awareness through outreach and advocacy, providing education and support services for patients, and funding research focused on prevention or cure. Such organisations carry important lobbying power among national governments and often contribute to policy discussions on key matters such as drug approval and insurance coverage. However, given increasing financial pressures, many groups receive corporate funding from pharmaceutical and device companies, which poses a potential conflict of interest. In the linked paper (above), Mandeville and colleagues examine the financial interests of patient organisations contributing to health technology assessments, at NICE.[1]

Through this innovative approach, the authors determined that more than two thirds of patient organisations contributing to appraisal of a technology received funding from that technology's manufacturer or the manufacturer of a competitor technology within the previous year. NICE's decision making committees were aware of less than a quarter of these potential financial conflicts of interests. For nearly two thirds of the interests of which committees were unaware, disclosure was not required by NICE's current policy.[1]

Widespread problems

These findings contribute substantively to the broader picture of the influence of industry in patient organisations. International studies echo these findings, suggesting that a substantial number of patient organisations have potential financial conflicts of interest but limited disclosure practices.[2-6] Mandeville and colleagues add a valuable perspective to this discourse by illuminating the role these conflicts of interest may play in government decision making on healthcare in England. Limited research on decision making by the US Food and Drug Administration and the European Medicines Agency suggests that this problem is unfortunately widespread.[7-9]

That most patient organisations did not voluntarily disclose potential conflicts of interests on Disclosure UK, online, or through the researcher's follow-up inquiry is surprising and raises concerns about voluntary self disclosure as a realistic or effective method of appropriately managing these organisations' conflicts of interest.

Reviews of Disclosure UK, the database recording payments from companies in the Association of the British Pharmaceutical Industry to healthcare professionals and organisations, has shown that the recipients most likely to opt out are those receiving the largest payments, and thus the most likely to have substantial financial conflicts of interest.[10 11]

Countries must confront the critical question of how to manage disclosure of interests by patient organisations that contribute to government decision making

Recognising these concerns, the US and several European countries have moved towards mandatory disclosure through various "sunshine" acts meant to increase transparency,[12 13] leaving some people clamouring for the UK to do the same.[10 14] However, patient organisations are often not included in these disclosure laws, including those in the US. Beyond disclosure to

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Specific interests and disclosure to NICE's committees. Values are numbers (percentages)

Proportion	Funding from ≥1 manufacturer of: Technology under appraisal	Competitor product(s)	Total specific interests
Patient organisations with specific interests	34/53 (64)	34/53 (64)	38/53 (72)
Occasions with specific interests present	73/117 (624)	71/117 (61)	92/117 (79)
Specific interests known to NICE's committees out of all declarable specific interests*	18/39 (46)	12/34 (35)	30/73 (41)‡
Specific interests unknown to NICE's committees out of all unknown specific interests†	34/55 (62)	37/59 (63)	71/114 (62)‡
Specific interests known to NICE's committees out of all specific interests identified	18/73 (25)	12/71 (17)	30/144 (21)‡

*Denominator includes only specific interests in which nominated patient experts were employees, trustees, or medical directors of patient organisations. These people would be expected to declare their organisation's interests as indirect interests.

†NICE's policy requires declaration of indirect interests only by nominated experts as above and not for other types of contributions by patient organisations.

‡Each specific interest is counted separately, so values are sum of first two columns rather than number of occasions.

the general public through a national database, England and other countries must confront the critical question of how to manage disclosure of interests by patient organisations that contribute to government decision making in health.

When pharmaceutical and device companies lobby government leaders or participate in government decision making, their for-profit incentives are typically clearly visible; however, when patient organisations participate in similar activities, government leaders and members of the public may believe them to be unbiased and acting independently in the best interests of patients they represent.[15]

For NICE (and its counterparts in other countries) to better judge and interpret recommendations made by patient organisations, its policies must require disclosure in all circumstances and not just in the nomination of patient and clinical experts. Furthermore, NICE must ensure complete enforcement with compliance from all patient organisations.

Meaningful response

Finally, once patient organisations achieve full transparency, how should NICE and similar organisations interpret and respond to their declared conflicts of interest? According to Mandeville and colleagues, almost all of the nominated patient and clinical experts who declared financial conflicts of interest were selected to attend NICE committee meetings. Furthermore, similar proportions of those declaring and not declaring conflicts attended NICE meetings.[1]

Disclosure alone is not a robust enough safeguard to ensure public trust, and extra legislation and organisational policies are needed for all stakeholders to react in a meaningful way to the information disclosed.[15]

Cite this as: *BMJ* 2019;364:l129

Find the full version with references at http://dx.doi.org/10.1136/bmj.l129

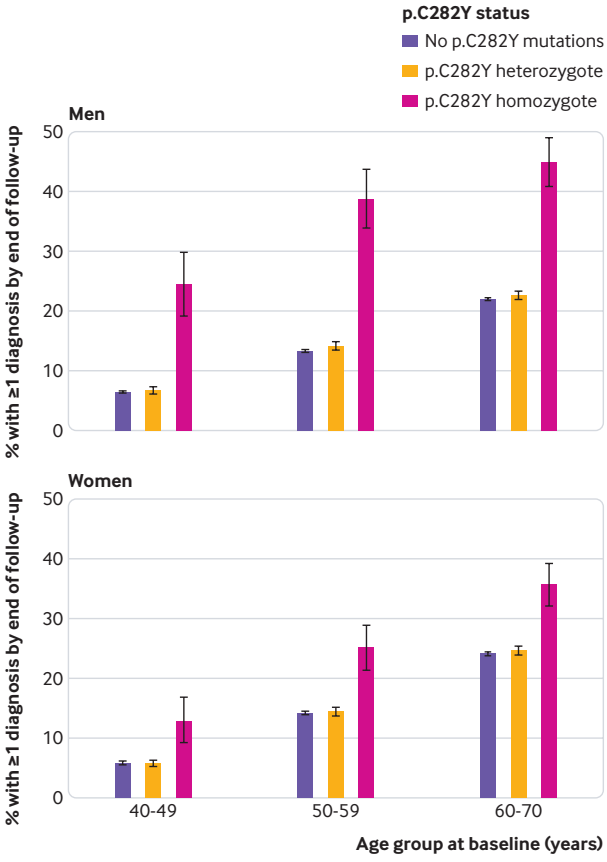
MALCOLM WILLETT

Common conditions associated with hereditary haemochromatosis genetic variants

Pilling LC, Tamosauskaite J, Jones G, et al

Cite this as: *BMJ* 2019;364:k5222
Find this at: http://dx.doi.org/10.1136/bmj.k5222

Study question What is the excess clinical morbidity in people with the *HFE* p.C282Y genetic variant (responsible for most hereditary haemochromatosis type 1) compared with those with no p.C282Y mutations?



Percentage of participants with one associated diagnosis or more by HFE p.C282Y genotype, baseline age group, and sex. Included diseases were haemochromatosis; any liver disease, including liver cancer; diabetes types 1 and 2; osteoarthritis; or rheumatoid arthritis. Whiskers represent 95% confidence intervals

Methods The cohort comprised 451 243 community based participants of European descent from UK Biobank aged 40 to 70 years at baseline, with a mean follow-up of seven years (mean age 63.8 years at end of follow-up). The authors compared prevalent and incident morbidity and mortality between those with the *HFE* p.C282Y genetic variant and those with no p.C282Y mutations. Odds ratios and Cox hazard ratios of disease rates between participants with and without the haemochromatosis mutations were adjusted for age, genotyping array type, and genetic principal components.

Study answer and limitations Of 2890 participants homozygous for p.C282Y (0.6%, or 1 in 156), haemochromatosis was diagnosed in 21.7% (95% confidence interval 19.5% to 24.1%, 281/1294) of men and 9.8% (8.4% to 11.2%, 156/1596) of women by end of follow-up. Male p.C282Y homozygotes had higher odds ratios for baseline haemochromatosis, any liver disease, diabetes, osteoarthritis, or rheumatoid arthritis and a higher incidence of these diagnoses during follow-up (all P<0.001). At end of follow-up, 1 in 5 more p.C282Y homozygote men (22.6%, 95% confidence interval 19.9% to 25.2%, P<0.001) and 1 in 10 more homozygote women (10.6%, 8.4% to 12.8%, P<0.001) had diagnoses of any liver disease, diabetes, osteoarthritis, or rheumatoid arthritis, compared with those without mutations. In male participants, 1.6% of all baseline hip replacements and 5.8% of incident liver cancers were in p.C282Y homozygotes. Limitations of the study were that the authors studied volunteers from the community, although genotype prevalence was similar to that of previous reports, and disease incidence alone indicates substantial excess morbidity. Lifetime penetrance would be higher. No serum iron related measures were available.

What this study adds People who are homozygotes for the p.C282Y mutation responsible for hereditary haemochromatosis type 1 often have excess morbidity. As treatment (venesection) is safe and effective if started early, issues involved in offering screening and improving early case ascertainment for p.C282Y homozygotes need re-examining.

Funding, competing interests, and data sharing This study was mainly supported by Medical Research Council grant (MR/M023095/1) to the principal investigator, David Melzer. No competing interests declared. Data are available from UK Biobank.