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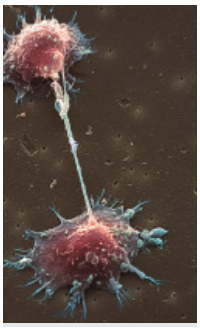

Most EMA approved cancer drugs marketed in 2009-13 lacked evidence of benefit on survival or quality of life
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New QMortality equation provides measure of absolute risk of death in older patients
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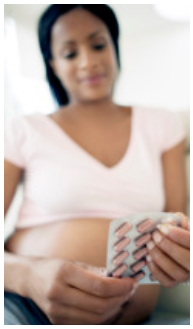

Maternal multivitamin use associated with lower odds of ASD with intellectual disability in offspring
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ORIGINAL RESEARCH Retrospective cohort study of drug approvals 2009-13

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency

Davis C, Naci H, Gurpinar E, et al

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Study question What proportion of cancer drugs approved in Europe are associated with gains in survival and quality of life, and are any benefits present clinically meaningful?

Methods Retrospective cohort analysis of the evidence base for cancer drugs approved by the European Medicines Agency (EMA) 2009-13, and evaluation of the magnitude of clinical benefit with the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). The authors reviewed publicly accessible regulatory and scientific reports.

Study answer and limitations From 2009 to 2013, the EMA approved the use of 48 cancer drugs in 68 indications. Eight of these approvals were based on results of a single arm study. Of the 68 approved uses, and with a median of 5.4 years' follow-up, there was a significant improvement in survival or quality of life over active treatment or placebo for only 35 (51%). Of 23 indications in which there was a survival benefit that could be scored with the ESMO-MCBS tool, the benefit was judged to be clinically meaningful in less than half (11/23, 48%). These analyses did not consider the appropriateness of specific aspects of clinical trial design and analysis and could have overestimated the proportion of drugs that offer survival or quality of life gains and the clinical relevance of these for patients.

Characteristics of the cohort of cancer drug approvals, 2009-13

Outcomes	No (%)	
	Solid tumours (n=51)	Haematological tumours (n=17)
Type of marketing authorisation:		
First marketing authorisation	24 (47)	9 (53)
Extension	27 (53)	8 (47)
Pathway of first marketing authorisation:		
Regular approval	19 (79)	4 (44)
Conditional approval	5 (21)	5 (56)
Orphan designation	3 (6)	8 (47)
Intent of therapy:		
Curative	6 (12)	1 (6)
Non-curative	45 (88)	16 (94)

What this study adds No recent studies have systematically examined the evidence base and magnitude of benefit for cancer drugs approved by the EMA. This study shows that most new oncology drugs authorised by the EMA in 2009-13 have not been shown to improve survival or quality of life and that when survival gains are shown they are not always clinically meaningful.

Funding, competing interests, data sharing This study was supported by project funding from Health Action International (HAI). One author is a member of HAI Europe Members Association, and another is a board member of HAI Europe. No additional data available.

COVER STORY, p 12

Identifying frailty in primary care

ORIGINAL RESEARCH Cohort study

Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty

Hippisley-Cox J, Coupland C

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Find this at: http://dx.doi.org/10.1136/bmj.j4208

Performance of QMortality algorithm to predict one year risk of death, and QAdmissions score to predict risk of unplanned admission over one year in men and women aged 65-100 years in validation cohort

	Mean (95% CI)	
Statistics	**Women**	**Men**
QMortality score:		
D statistic	2.29 (2.27 to 2.31)	2.18 (2.16 to 2.20)
Harrell's C	0.853 (0.850 to 0.856)	0.844 (0.841 to 0.847)
R^2 (%)	55.6 (55.2 to 56.0)	53.1 (52.6 to 53.6)
QAdmissions score:		
D statistic	1.50 (1.49 to 1.51)	1.45 (1.44 to 1.46)
Harrell's C	0.757 (0.755 to 0.759)	0.751 (0.748 to 0.753)
R^2 (%)	34.9 (34.5 to 35.2)	33.5 (33.0 to 33.9)

Study question How can we best predict the short term risk of death and develop a new classification method for frailty based on risk of death and risk of unplanned hospital admission?

Methods This cohort study used routinely collected data from 1436 general practices contributing to the QResearch database. 1079 practices were used to develop the scores and a separate set of 357 practices to validate the scores. 1.47 million patients aged 65-100 years were in the derivation cohort and 0.50 million patients in the validation cohort. The authors used Cox proportional hazards models to predict one year risk of death. Risk factors considered were age, sex, ethnicity, deprivation, smoking status, alcohol intake, body mass index, medical conditions, prescribed drugs, social factors, and investigations. Measures of calibration and discrimination were determined in the validation cohort. The mortality equation was used with QAdmissions (which predicts risk of unplanned hospital admission) to classify patients into frailty groups.

Study answer and limitations The final model included age, body mass index, Townsend deprivation score, ethnic group, smoking status, alcohol intake, unplanned hospital admissions, atrial fibrillation, antipsychotics, cancer, asthma or chronic obstructive pulmonary disease, living in a care home, congestive heart failure, corticosteroids, cardiovascular disease, dementia, epilepsy, learning disability, leg ulcer, chronic liver disease or pancreatitis, Parkinson's disease, poor mobility, rheumatoid arthritis, chronic kidney disease, types 1 and 2 diabetes, venous thromboembolism, anaemia, abnormal liver function test result, high platelet count, and consultations in the past 12 months for appetite loss, weight loss,

COMMENTARY Identifying a problem is acceptable only if there's an effective solution

Frailty is a common accompaniment to aging, bringing reduced resilience to acute problems compared with healthier people.[1] Recovery takes longer and is sometimes incomplete. Falls are frequent. Polypharmacy—much of it futile—is common.[2] In theory, if frail people could be identified, some of these problems could be averted. This is the rationale behind the requirement for general practitioners in England to identify severely frail people on their lists, to review them for risk of falls, and to ensure their treatment is suitable.[3]

In this issue, Hippisley-Cox and Coupland report a new predictive algorithm for short term mortality (QMortality).[4] They also develop a new classification of frailty, combining risk of death with risk of hospital admission (QFrailty categories), building on an existing electronic frailty index (EFI) from a similar English database, and a smaller Dutch study.[5 6]

> A substantial proportion of those identified by the EFI or QMortality would already be under regular review for chronic disease

Both English studies are large, are well conducted, and crucially use primary care data, unlike previous instruments.[7]

In the real world

Crucially, however, when either QMortality or the EFI is used to select the "worst 2%" of patients in a general practice, many patients are misclassified as being false positives or false negatives. It is also likely that a substantial proportion of those identified by the EFI or QMortality would already be under regular review for chronic disease. So, we have possibly helpful but imperfect tests. No primary care algorithm measures frailty directly.

If the QMortality and the QFrailty instruments were implemented, are doctors honest enough to say to a patient, "You're in the worst 2% for risk of death or unplanned hospital admission—let's discuss drugs and falls"? Patients are unlikely to welcome being placed among the worst 2%, especially if there is an even chance that the categorisation is wrong.

Patients are very receptive to early diagnosis if the benefit is clear, either for ameliorating symptoms or averting death.[8] When it comes to frailty, most patients are aware of their problems, and many are content to live within their limitations. Being told you are in the "mortality relegation zone" when there are few, if any, personal benefits available from intervention is much less attractive—arguably insulting.

Even if such terminology problems could be surmounted, how big are the benefits from interventions aimed at reducing polypharmacy and falls? A Dutch trial of a primary care programme to preserve daily function, using their frailty index, found small differences in favour of intervention,

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or breathlessness. The model had good calibration and high levels of explained variation and discrimination. For example, in women, the equation explained 55.6% of the variation in time to death (R^2), and had very good discrimination (D statistic 2.29; Harrell's C 0.85). By combining predicted risks of mortality and unplanned hospital admissions, 2.7% of patients (n=13 665) were classified as severely frail, 9.4% (n=46 770) as moderately frail, 43.1% (n=215 253) as mildly frail, and 44.8% (n=223 790) as fit.

What this study adds The authors have developed new equations to predict one year risk of death, taking account of demographic, social, and clinical variables. The equations performed well on a separate validation cohort. The QMortality equations can be used with the QAdmissions equations, to classify patients into four frailty groups (known as QFrailty categories) to identify those for further assessment.

Funding, competing interests, data sharing
No external funding was received for this study.
See full paper on bmj.com for other details.

but these were of doubtful clinical value.[9] A recent systematic review and meta-analysis of trials of de-prescribing in elderly patients reported no reduction in mortality, falls, or adverse events, nor did the review report any improvements in quality of life (other than in one trial), despite a decrease in the numbers of drugs used.[10] The optimum methods for de-prescribing in primary care are uncertain, as is the cost effectiveness.

In contrast, good evidence supports intervention to reduce falls: a systematic review of exercise programmes reported a pooled rate ratio for falls, leading to an injury in the exercise group, of 0.63 (95% confidence interval 0.51 to 0.77).[11] Other interventions to reduce falls—or mitigate their impact—such as vitamin D supplementation and hip protectors may also be cost effective.[12] Whether these interventions are best targeted at the worst 2% (however identified) is unknown. It is possible they would be better targeted at less frail patients.

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Poor timing

This all adds up to a problem for primary care, and particularly English primary care, with the new contractual obligation for general practitioners to identify all those on their list older than 65 years with severe frailty. Such a policy arguably fails on several of the classic Wilson and Jungner criteria for screening, including those relating to patient acceptability and cost effectiveness, let alone the suitability of the screening test.[13]

The timing is poor too. The number of general practitioners in the UK is stable or falling, yet workload increased by 16% between 2007-8 and 2013-14, and probably continues to rise.[4] This is not to downplay the importance of managing polypharmacy or falls. Even so, the existence of a problem such as frailty does not presuppose the existence of an effective solution—or even a flawed one.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j4478

Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort

DeVilbiss EA, Magnusson C, Gardner RM, et al

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Find this at: http://dx.doi.org/10.1136/bmj.j4273

Study question Is nutritional supplementation during pregnancy associated with a reduced risk of autism spectrum disorder (ASD) in offspring?

Methods A population based sample in Stockholm County, Sweden of 273 107 children born between 1996 and 2007 and their mothers was identified through population registers. Maternal use of multivitamins, iron, and folic acid supplements was reported at the first antenatal visit and diagnoses for ASD in children with and without intellectual disability were ascertained from register data through 2011. Adjusted odds ratios and 95% confidence intervals were estimated using sibling controls, propensity score matching, and multivariable regression.

Study answer and limitations Maternal multivitamin use with and without additional iron or folic acid, or both was associated with lower odds of ASD with intellectual disability in children compared with mothers who did not use multivitamins, iron, or folic acid (odds ratio 0.69, 95% confidence interval 0.57 to 0.84). The authors found similar estimates in propensity score (0.68, 0.54 to 0.86) and sibling control (0.77, 0.52 to 1.15) matched analyses, although the latter association was not statistically significant. Further scrutiny of maternal nutrition and its role in the cause of ASD with intellectual disability is warranted.

What this study adds Maternal multivitamin supplementation may be inversely associated with ASD with intellectual disability in offspring.

Funding, competing interests, data sharing This study was funded by the National Institutes of Health (1 R21 ES023760-01A1, Early life vitamin D levels and risk of autism spectrum disorders), Swedish Research Council, and National Institute for Health Research Biomedical Research Centre Bristol. The authors have no competing interests. The statistical code is available from the corresponding author.

Adjusted odds ratios (95% confidence intervals) for supplement use and autism spectrum disorder (ASD) with and without intellectual disability

Sample	Sibling adjusted*	Propensity score†	Multivariable adjusted‡
ASD with intellectual disability:			
Multivitamin	0.77 (0.52 to 1.15)	0.68 (0.54 to 0.86)	0.69 (0.57 to 0.84)
Iron	0.90 (0.67 to 1.21)	0.96 (0.82 to 1.13)	0.95 (0.83 to 1.11)
Iron and folic acid	0.99 (0.63 to 1.57)	1.06 (0.86 to 1.30)	1.03 (0.84 to 1.26)
Folic acid	0.94 (0.29 to 3.04)	1.14 (0.64 to 2.04)	1.20 (0.71 to 2.01)
ASD without intellectual disability:			
Multivitamin	1.00 (0.83 to 1.20)	0.95 (0.85 to 1.06)	0.94 (0.85 to 1.03)
Iron	0.96 (0.81 to 1.12)	0.95 (0.88 to 1.04)	0.96 (0.89 to 1.04)
Iron and folic acid	1.00 (0.78 to 1.29)	0.84 (0.74 to 0.94)	0.89 (0.79 to 1.00)
Folic acid	1.70 (0.94 to 3.10)	1.10 (0.83 to 1.48)	1.29 (0.99 to 1.67)

*Conditional logistic regression adjusted for child characteristics (sex and birth year) and parity.
†Propensity scores were calculated with covariates (see ‡) as predictors of supplement use in ordinary logistic regression models; in the matched sample, propensity scores were used as predictors of ASD in generalised estimating equation logistic regression models grouped by birth mother.
‡Generalised estimating equation logistic regression, grouped by birth mother; adjusted for child characteristics (sex, birth year, and years resided in Stockholm County), socioeconomic indicators (education, family income, and maternal birth country), maternal characteristics (age, body mass index, parity, smoking status), drug use during pregnancy (antidepressants or antiepileptics), and maternal neuropsychiatric conditions (anxiety disorders, autism, bipolar disorder, depression, epilepsy, intellectual disability, non-affective psychotic disorders, and stress disorders).