research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

Getting AI to eyeball the boring stuff

Pattern recognition is a big part of medicine. Some doctors such as radiologists and histopathologists spend whole working lives using their clever eyes and brains to convert visual images into diagnostic reports, and that is just what we humble generalists need in order to get anything done.

But increasingly, where there's a pattern there's a machine that can recognise it better than a human, using deep learning algorithms. The day may be fast approaching when the diagnostic "gold standard" for many routine kinds of image reporting won't be a panel of experts but a superior machine.

Here's a study of one that reads retinal photographs for signs of diabetic retinopathy. The dataset was based on more than 10 000 retinal images taken in several countries using different cameras, so there is a lot of complex data in this report. But overall it looks as if the automated machine with its "deep neural network" learning system achieved sensitivity and specificity levels at least as good as any single human reader. Compared with a panel of at least seven ophthalmologists for each image across the whole dataset, the algorithm could be ratcheted up to achieve 98% levels for either, according to how you set it. In the future it seems likely that ophthalmologists will be trained and assessed by machines, and not the other way round.

JAMA 2016, doi:10.1001/jama.2016.17216

Can genes prove how drugs work?

Medicine is the application of neat science to a messy world. We love it when it works simply—for example, when a single gene controls a single biochemical process that we can then block with a single chemical.

Statins are often cited as an example: they block 3-hydroxy-3-methylglutaryl–coenzyme A reductase, an enzyme that is governed by the HMGCR gene. By doing so statins reduce circulating levels of low density lipoprotein cholesterol and, bingo, down goes your cardiovascular risk. But for less obvious reasons they also increase blood glucose levels slightly and cause muscle symptoms in many people. If your glucose concentration is highish to start with, statins may cause you to "get diabetes,"—that is, you cross an artificial threshold and are bundled together with millions of different people with this scary label.

But can all this really be put down to the HMGCR gene? Here's a population study that concludes it can, provided you throw in a second gene locus governing low density lipoprotein cholesterol levels. This is the PCSK9 gene, which controls the expression of proprotein convertase subtilisin-kexin type 9. If you look at natural variants of these two gene loci in a large population, you'll find exactly what the theory predicts: the level of gene expression correlates with the level of cardiovascular risk which correlates with the level of low density lipoprotein cholesterol, and there is a small increase in blood glucose concentrations in those on the "diabetic" borderline. So does this mean that PCSK9 inhibitors will inevitably prove as or more effective than statins for long term cardiovascular protection in adults without symptoms? The science is neat but the world is messy. We might know for sure in 10-15 years. Oh, and I mentioned muscle effects. Maybe it's high time to look prospectively for those, in both drug classes. And this study needs replication in other populations. Medical science is actually never simple.

N Engl J Med 2016, doi:10.1056/NEJMoa1604304

Two is as good as three for HPV

Although vaccination has done more good to the world than any other medical intervention, it is still important to treat each new mass vaccination programme as a human experiment on a large scale. Once again the science is simple but the world is complex. In the case of vaccination against human papillomaviruses transmitted sexually and associated with anal, cervical, and oropharyngeal cancers, we are awaiting the long term reductions in these conditions, which ought to follow elimination of the viruses; and the results are promising.

No adverse effects have emerged when teenage populations have been vaccinated, whereas viral transmission has fallen even more dramatically than expected. The question of how many doses are needed is now also practically settled: this trial across 52 sites in 15 countries confirms that two shots of nine valent vaccine provide lasting immunogenicity. This is already standard practice in a number of countries, and the accompanying editorial (doi:10.1001/jama.2016.16393) gives a good summary of the current position.

JAMA 2016, doi:10.1001/jama.2016.17615

Goal driven care for dementia

Dying slowly from dementia in a nursing home is a common alternative to dying from cancer or cardiovascular disease. Many of us, dear readers, will end our lives this way. Hopefully we'll have lost awareness, but our loved ones will come to us day by day hoping for a flicker of recognition and wondering how this will end and how soon.

At least they should know that a care plan exists that takes into account patients' goals and wishes, and I think this is now pretty universally the case in the UK. In case you need trial evidence that this is not just the right thing to do but also achieves better outcomes in the USA, here it is. The goals of the care decision aid they tested resulted in better communication, more involvement from palliative care, and fewer hospital admissions.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.7031

Communicating risk to emergency department patients

ORIGINAL RESEARCH Prospective randomised pragmatic trial

Shared decision making in patients with low risk chest pain

Hess EP, Hollander JE, Schaffer JT, et al

Cite this as: *BMJ* 2016;355:i6165
Find this at: http://dx.doi.org/10.1136/bmj.i6165

Study question How effective is shared decision making compared with usual care in the choice of admission for further cardiac testing or referral for outpatient evaluation in patients with possible acute coronary syndrome?

Methods This was a multicentre parallel randomised controlled trial conducted in six US emergency departments. The researchers enrolled adults (aged >17 years) with a primary complaint of chest pain who were being considered for admission to an observation unit for cardiac testing. Patients were randomly assigned (1:1) to shared decision making facilitated by a decision aid ("chest pain choice") or to usual care. The primary outcome, selected by patient and caregiver advisers, was patients' knowledge about their risk of acute coronary syndrome. Secondary outcomes were involvement in the decision to be admitted, proportion of patients admitted for cardiac testing, and the 30 day rate of major adverse cardiac events (MACEs).

Study answer and limitations Compared with usual care, patients assigned to the decision aid arm had greater knowledge about their risk of acute coronary syndrome (questions correct: 4.2 *v* 3.6; mean difference 0.66, 95% confidence interval 0.46 to 0.86), were more involved in the decision (observing patient involvement scores: 18.3 *v* 7.9; mean difference 10.3, 9.1 to 11.5), and less frequently decided to be admitted for cardiac testing (37% *v* 52%; absolute difference 15%; P<0.001). No MACEs occurred due to the intervention. Use of a decision aid in patients at low risk of acute coronary syndrome increased patient knowledge and engagement and decreased the rate of admission to an observation unit for cardiac testing. The trial was underpowered to definitively show safety (MACEs).

What this study adds Translating validated risk estimates to practice and engaging patients in care decisions through shared decision making might tailor testing to disease risk in a way that is acceptable to patients, clinicians, and policy makers.

Funding, competing interests, data sharing The study was funded by the Patient Centered Outcomes Research Institute (contract 952). JEH has research funding from Alere, Trinity, Siemens, and Roche and has consulted for Janssen. DBD has research funding from Siemens and Roche and has consulted for Janssen. A link to the probability web tool and the decision aid is at http://shareddecisions.mayoclinic.org/decision-aid-information/chest-pain-choice-decision-aid/.

Study registration ClinicalTrials.gov NCT01969240.

COMMENTARY Shared decision making works well even in this highly charged setting

"Nothing about me without me"[1] and "Really putting patients at the centre of healthcare"[2] are just two expressions of the call for patient involvement and shared decision making. For many, shared decision making is becoming the norm, but for others it is seen as just a fashionable phrase, to be followed by business as usual. In a linked report of a study involving patients at all stages from study design to publication, Hess and colleagues took up the challenge of supporting patient decision making in the emergency department.[4] Using a "quantitative pretest probability webtool" built into a decision aid, the authors more than doubled patient involvement, increased patient knowledge, and reduced hospital admissions for cardiac testing.

The rationale for the study was the substantial burden and cost associated with admission for suspected acute coronary syndrome. The authors argue that despite a decrease in emergency department visits for and diagnosis of acute coronary syndrome over the past decade, use of advanced imaging increased almost fourfold. In an earlier survey, the authors found a strong aversion among clinicians to the risk of missing an acute myocardial infarction: almost 60% of emergency department clinicians considered a 1% miss rate for myocardial infarction and associated major adverse cardiovascular events unacceptable.[5]

This study supports the view that giving patients more information about risk is not to be feared

With an average pretest probability of acute coronary syndrome of just under 4% in the current study, communicating this probability to patients led to a one third reduction in admissions. Patients may be less risk averse than clinicians: they are willing to forego admission at a level of risk three or four times higher than clinicians consider acceptable. These results are in line with others showing that providing patients with decision aids often leads to more conservative decisions compared with usual care.[6]

Proponents of shared decision making could therefore ally more strongly with *The BMJ*'s "Too Much Medicine" initiative and the Preventing Overdiagnosis movement.[7] The degree to which sharing decisions "may act as a brake on overdiagnosis, overtreatment, and iatrogenic harm"[8] is still unclear, but it might be substantial, as the study by Hess and colleagues suggests.

A central component of Hess and colleagues' intervention was an attribute matching tool estimating patients' 45 day risk for acute coronary syndrome. Part of the observed effect will likely have been due to the availability of that risk estimate, leading to a different conversation, in which patients become more knowledgeable about their prognosis. A major drawback of the decision aid is that it required eight patient variables, collected and keyed in by a study coordinator. This complexity could hamper large scale implementation.

Owing to lack of power the authors caution that "a large scale implementation trial is needed to definitively assess safety." Nevertheless, this study supports the view that giving patients more information about risk is not to be feared—on the contrary, sharing this information may well benefit both patients and healthcare systems.

Anne M Stiggelbout a.m.stiggelbout@lumc.nl
J Wouter Jukema; Ellen E Engelhardt; Carla van den Bos; Arwen H Pieterse. See thebmj.com for author details

Cite this as: *BMJ* 2016;355:i6437
Find this at: http://dx.doi.org/10.1136/bmj.i6437

Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia

Dulai PS, Singh S, Marquez E, et al

Cite this as: *BMJ* 2016;355:i6188
Find this at: http://dx.doi.org/10.1136/bmj.i6188

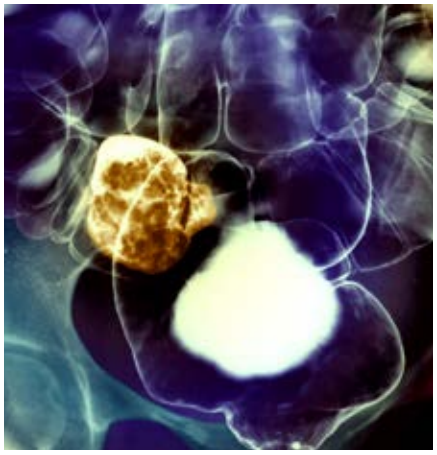
Study question What is the comparative efficacy and safety of candidate agents (low and high dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), calcium, vitamin D, folic acid, alone or in combination) for preventing advanced metachronous neoplasia (that is, occurring at different times after resection of initial neoplasia) in individuals with previous colorectal neoplasia?

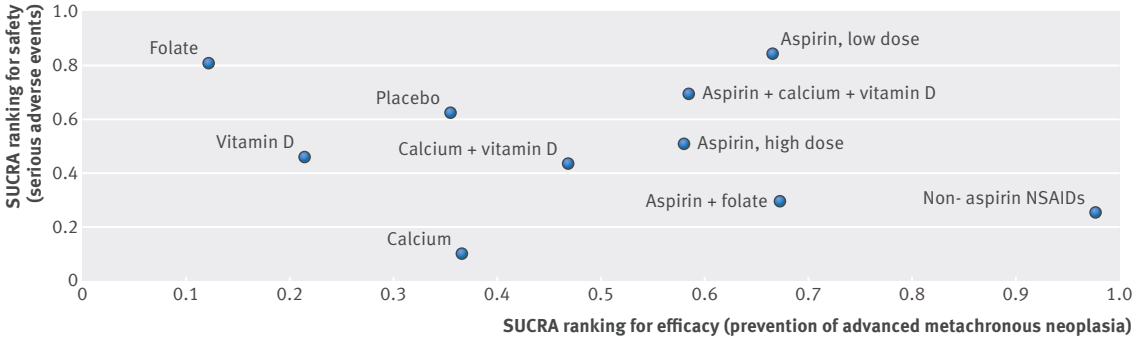
Methods Systematic literature review of multiple electronic databases to 15 October 2015 identified 14 randomised controlled trials in adults with previous colorectal neoplasia, treated with candidate chemoprevention agents, and compared with placebo or another candidate agent. Primary efficacy outcome was risk of advanced metachronous neoplasia; safety outcome was serious adverse events. A Bayesian network meta-analysis was performed and relative ranking of agents was assessed with surface under the cumulative ranking (SUCRA) probabilities. Quality of evidence was appraised with GRADE criteria.

Study answers and limitations Compared with placebo, non-aspirin NSAIDs were ranked best for preventing advanced metachronous neoplasia (odds ratio 0.37, 95% credible interval 0.24 to 0.53; SUCRA=0.98) (high quality evidence), followed by low dose aspirin (0.71, 0.41 to 1.23; SUCRA=0.67) (low quality evidence). Low dose aspirin, however, was ranked the safest among chemoprevention agents (0.78, 0.43 to 1.38; SUCRA=0.84), whereas non-aspirin NSAIDs (1.23, 0.95 to 1.64; SUCRA=0.26) were ranked low for safety. High dose aspirin was comparable with low dose aspirin in efficacy (1.12, 0.59 to 2.10; SUCRA=0.58) but had an inferior safety profile (SUCRA=0.51). Because of the small number of events, efficacy of agents for reducing metachronous colorectal cancer could not be estimated.

What this study adds Among people with previous colorectal neoplasia, non-aspirin NSAIDs are the most effective agents for preventing advanced metachronous neoplasia, whereas low dose aspirin has the most favourable risk:benefit profile.

Funding, competing interests, data sharing No direct funding. The authors have received funding for other projects (see thebmj.com). Technical appendix, statistical code, and dataset available from the corresponding author.
Registration This systematic review has been registered at PROSPERO (CRD42015029598).


SPL



SUCRA rankings for efficacy and safety outcomes (range 1=treatment has high likelihood of being best, 0=treatment has high likelihood of being worst). For efficacy outcomes, higher score=better treatment for preventing advanced metachronous neoplasia. For serious adverse event outcome, higher scores=safer treatment with lower risk of serious adverse events. Table shows median ranks on both efficacy and safety outcomes (rank 1-10 on each scale) and 95% credible intervals

Agent	Placebo	Folate	Calcium	Vitamin D	Non-aspirin NSAIDs	Aspirin, low dose	Aspirin, high dose	Aspirin + folate	Calcium + vitamin D	Aspirin + calcium + vitamin D
Efficacy rank (95% CrI)	7 (4 to 9)	9 (5 to 10)	7 (3 to 10)	9 (3 to 10)	1 (1 to 2)	3 (2 to 9)	5 (2 to 9)	4 (2 to 8)	6 (1 to 10)	3 (1 to 10)
Safety rank (95% CrI)	4 (2 to 7)	2 (1 to 7)	10 (6 to 10)	6 (1 to 10)	8 (3 to 10)	2 (1 to 9)	5 (2 to 10)	8 (3 to 10)	6 (2 to 10)	3 (1 to 10)

Development and validation of risk prediction model for venous thromboembolism in postpartum women

Abdul Sultan A, West J, Grainge MJ, et al

Cite this as: *BMJ* 2016;355:i6253
Find this at: http://dx.doi.org/10.1136/bmj.i6253

Study question Can a risk prediction tool to estimate the risk of venous thromboembolism in the first six weeks after childbirth be developed and externally validated?

Methods Two large national cohorts of postpartum women from England and Sweden were analysed to predict the occurrence of first venous thromboembolism within the first six weeks after childbirth. For model development, postpartum women with no history of venous thromboembolism were identified from England's Hospital Episode Statistics linked to the Clinical Practice Research Datalink between 1997 and 2014 (433 353 deliveries). External validation used the Swedish medical birth and patient registries to identify a comparable population between 2005 and 2011 (662 387 deliveries).

Summary answer and limitations The absolute rate of venous thromboembolism was 7.2 per 10 000 deliveries in the English cohort and 7.9 per 10 000 in the Swedish cohort. A model has been developed and externally validated that can be used to calculate the absolute predicted risk of venous thromboembolism during the postpartum period. It cannot be used for women with one or more risk factors not measured in the model and should not be solely relied on for prescribing thromboprophylaxis.

What this paper adds The externally validated prediction model identifies women at high risk on the basis of their absolute predicted risk of venous thromboembolism in the first six weeks postpartum and can be used at point of care after delivery. This is based on data obtained from a representative sample of deliveries from the UK and Sweden and could be used to set treatment thresholds based on absolute risk of individual women rather than heterogeneous ordinal categories.

Comparing current guidelines with risk prediction model

	English data (n=433 353 postpartum women; n=312 VTE events)		Swedish data (n=662 387 pregnancies; n=521 VTE events)	
Statistics	**UK guideline**	**Risk prediction model***	**Swedish guideline**	**Risk prediction model†**
Total No (%) warranting thromboprophylaxis	149 402 (34.5)	149 402 (34.5)	41 254 (6.2)	41 254 (6.2)
Observed VTE events	197	212	109	158
Mean predicted risk per 10 000 pregnancies	12.3	13.0	25.8	31.6
Sensitivity, % (95% CI)	63.1 (57.5 to 68.5)	67.9 (62.5 to 73.1)	20.9 (17.5 to 24.7)	30.3 (26.4 to 34.5)
Positive predictive value, % (95% CI)	0.13 (0.11 to 0.15)	0.14 (0.12 to 0.16)	0.26 (0.21 to 0.31)	0.38 (0.32 to 0.45)
Specificity, % (95% CI)	65.6 (65.4 to 65.7)	65.6 (65.4 to 65.7)	93.8 (93.7 to 93.8)	93.8 (93.7 to 93.9)

VTE=venous thromboembolism.
*Top 35% cut-off (threshold=6.3 per 10 000 deliveries).
†Top 6% cut-off (threshold=18 per 10 000 deliveries).

Study funding/potential competing interests This project was funded by JW's University of Nottingham/Nottingham University Hospital's NHS Trust senior clinical research fellowship. See thebmj.com for competing interests.

The BMJ is an Open Access journal. We set no word limits on *BMJ* research articles, but they are abridged for print.

The full text of each *BMJ* research article is freely available on thebmj.com.

The online version is published along with peer and patient reviews for the paper, and a statement about how the authors will share data from their study. It also includes a description of whether and how patients were included in the design or reporting of the research.

The linked commentaries in this section appear on thebmj.com as editorials. Use the citation given at the end of commentaries to cite an article or find it online.