SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

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Selected US adults look untroubled by genetic profiling

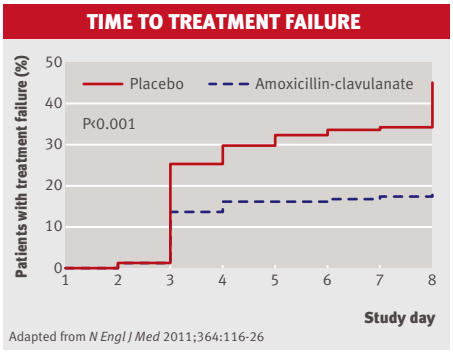
Genetic profiling is a growing industry that sells the promise of a glimpse into the future to any adult who can afford a test. The industry is unregulated, and the tests are unvalidated. Some experts believe they are unreliable, inaccurate, and clinically meaningless. But do they do any psychological harm?

In one study, a large cohort of US adults looked unfazed by commercial testing that quantified the lifetime risk of 23 different diseases including prostate cancer, breast cancer, abdominal aneurysm, obesity, and macular degeneration. The authors found little evidence of additional distress or anxiety three months after the test, even for those with positive results. Participants did not rush out for more screening tests, and only one in 10 asked for genetic counselling, which was provided free of charge. Genetic profiling had no discernible effect on fat intake or exercise. A quarter of the cohort shared their results with a doctor.

This uncontrolled study included a convenience sample of 3639 volunteers, mostly employees of health or technology companies and their families. They were well educated, wealthy, insured, and selected to resemble the kind of people targeted by companies selling genetic profiling. Follow-up was short. The effect of these tests on more vulnerable populations, or on anyone in the long term, remains unknown.

N Engl J Med 2011; doi:10.1056/nejmoa1011893

Antibiotics improve outcomes in young children with otitis media



Two new placebo controlled trials have confirmed that young children with definite otitis media get better faster when treated early with amoxicillin-clavulanate. They also have more side effects, including diarrhoea and nappy rash.

One commentator believes these trials lay to rest any lingering doubts about the use of antibiotics for young children with confirmed middle ear infections (p 168). Both trials recruited children with clear symptoms and signs including a middle ear effusion, an acutely inflamed tympanic membrane, fever, earache, respiratory symptoms, or other behaviours such as persistent crying or tugging at the ears. All 610 children were aged between 6 months and 3 years and evaluated by experienced otoscopists.

One trial tested higher doses of amoxicillin and clavulanate for 10 days. The other tested lower doses for seven days. Both were double blind. Authors reported significantly more treatment failures among placebo controls in both trials (51% *v* 16%; P<0.001 and 44.9% (71/158) *v* 18.6% (30/161); P<0.001). One also reported a significantly lower burden of symptoms among treated children.

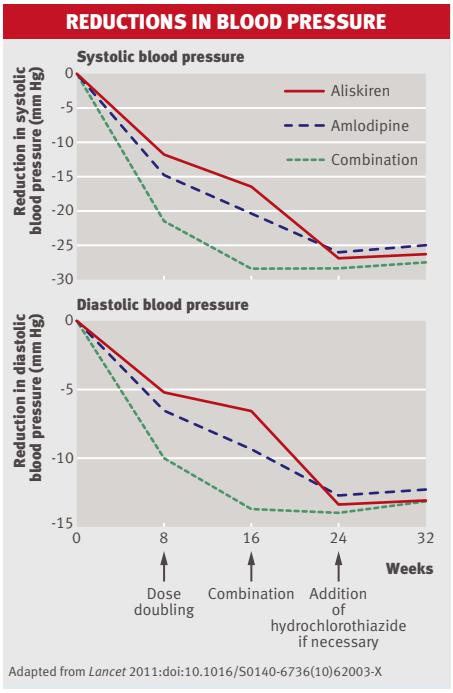
Almost half the treated children in one trial (47.8% (77/161)) and a quarter in the other (25%, (36/144)) had diarrhoea.

N Engl J Med 2011;364:105-15, 116-26

Two antihypertensives work better than one

First line treatment for hypertension can include one drug or two. Opinion is divided about which strategy is safest and most effective, despite multiple small trials and at least one meta-analysis. The latest trial evaluated first line treatment with aliskiren and amlodipine and was sponsored by Novartis. The results suggest that blood pressure falls further and faster in patients given this combination from the outset, compared with controls given one or other drug as monotherapy first. In an unusual design, the participants received one or two drugs for 16 weeks, then the monotherapy groups switched to the combination for a further eight weeks. The combination was clearly more effective for the first 16 weeks. After the switch, the other two groups began to catch up. But by 24 weeks those who started on the combination still had lower systolic (−1.9, 95% CI −3.7 to 0.0 mm Hg) and diastolic (−1.4, 95% CI −2.5 to −0.3 mm Hg) blood pressure than those who started on amlodipine alone. Analyses of responders also favoured the combination, for at least 16 weeks.

The researchers and a linked editorial (doi:10.1016/S0140-6736(10)62270-2) now



believe combination treatment is the best way to control blood pressure from the start and guidelines should move in that direction, if they haven't already. The benefits of this particular combination look clinically relevant and seem to last, extending to 32 weeks in one responder analysis. Patients taking both drugs reported no more serious side effects, including orthostatic hypotension, than controls starting with one.

Other first line combinations should now be tested, and researchers from the British Hypertension Society, who collaborated on the current trial, have already launched an independent evaluation of losartan combined with hydrochlorothiazide. We will have to wait until 2013 for the results.

Lancet 2011; doi:10.1016/S0140-6736(10)62003-X

Escitalopram helps a little with hot flushes

Women with menopausal hot flushes were left with few treatment options when new risks associated with hormone therapy emerged from large trials. Researchers are currently investigating antidepressants as an alternative, and there is some evidence that they work better than placebo. In the most recent trial, women taking escilatopram for eight weeks reported significantly greater reductions in symptoms than those taking placebo,

"Single combat between mounted Mongolian warlords and arguments between cardiac surgeons—these are spectator sports that it is best not to stand too close to"
Richard Lehman's journal blog at bmj.com/blogs

and symptoms returned when treatment stopped. Absolute differences were small, however, thanks to a powerful placebo effect. Daily frequency of hot flushes fell from 9.9 to 5.3 in women given escitalopram (−4.60, 95% CI −5.47 to −3.74) and from 9.7 to 6.4 in controls given placebo (−3.20, −4.15 to −2.24)—a difference of just 1.41 episodes a day (95% CI 0.13 to 2.69). Severity scores also fell in both groups during the trial. Scores on a three point scale fell 0.22 points further in women given escitalopram (−0.40 to −0.05). Side effects such as tiredness were common in both groups, but only nine women discontinued their treatment, including seven taking escitalopram.

These results are broadly in line with expectations. Escitalopram helps, but probably not as much as hormone therapy, say the authors, who recommend a head to head trial next. The mechanism of action remains unknown, but escitalopram seemed to work much faster for hot flushes than it would for anxiety or depression. In this trial, treatment effects were noticeable within a week.
JAMA 2011;305:267-74

Look harder for biomarkers for Alzheimer's disease

Alzheimer's disease is poorly understood, hard to diagnose, and even harder to treat. We urgently need a good biomarker and an accurate means to measure it. Two candidates are under scrutiny in recent studies—positron emission tomography (PET), which identifies β amyloid in the brain, and a blood test that measures β amyloid concentrations in plasma.

In the first study, PET imaging with an experimental ligand correctly identified the presence and quantity of β amyloid in the brains of 35 adults who were scanned near the end of life and then had a postmortem. Half were known to have Alzheimer's disease. In the second study, researchers measured β amyloids 40 and 42 in plasma samples from 997 healthy US adults with a mean age of 74. The ratio of the two types of β amyloid (42:40) was associated with cognitive decline over nine years. Lower ratios were associated with greater decline, particularly in those with a poor cognitive reserve at baseline.

Both studies are a good start, says one commentator (p 304). But we have a long way to go before either measure reaches the clinic, if they ever do. Biomarkers must be rigorously evaluated, just like drug treatments. Researchers should not be too seduced by the glamour of a new test to ignore essential but much more boring considerations of study design. The stakes are high and time is running out, she writes. An estimated one in four of us will ultimately develop Alzheimer's disease.
JAMA 2011;305:261-66, 275-83

Lady health workers save newborn lives in rural Pakistan

Community health workers known as "lady health workers" have been operating in rural Pakistan since 1994, providing family planning, antenatal care, immunisations, and other services to local communities. They are ideally placed to improve pregnancy outcomes, so researchers placed lady health workers at the centre of an initiative to reduce perinatal and neonatal mortality. They received extra training in antenatal and perinatal care, clean delivery kits to use, and were encouraged to visit pregnant women more often before and after delivery. Lady health workers forged relationships with traditional birth attendants, delivered group education to local women, encouraged births in health facilities, and helped set up voluntary health committees in villages. The whole package reduced stillbirths by 21% (risk ratio 0.79, 95% CI 0.68 to 0.92) and neonatal mortality by 15% (0.85, 0.76 to 0.96) in a cluster randomised trial. This means that it is feasible and effective to deliver new and life saving care through existing public sector health services in rural Pakistan, say the authors.

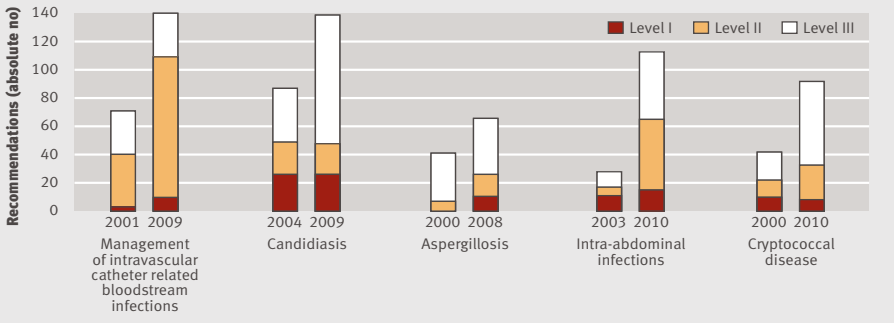
Results could have been even better. The intervention was complex and hard to implement. Poor infrastructure, resource constraints, and local politics took their toll on some elements of care, most notably the extra postnatal visits. Lady health workers managed to examine just 24% of 12 028 live births in intervention clusters.
Lancet 2011; doi:10.1016/S0140-6736(10)62274-X
Cite this as: *BMJ* 2011;342:d313

Guidelines should come with a health warning

The Infectious Diseases Society of America lists 52 current guidelines on its website. When researchers took a closer look at 41 of them, they found that just 14% (581/4218) of all recommendations were based on evidence from randomised trials. More than half the recommendations (55% (2330/4218)) were based on the shifting sands of expert opinion and anecdote. The strongest level A recommendations did slightly better (23% from trial evidence, 37% from expert opinion), but the authors still warn doctors not to suspend their own critical faculties when using these guidelines. Valuable though they are, guidelines can be only as good as the evidence they summarise, which is often poor. Others have reported similar results from different specialties, including cardiology.

More research of better quality would help says an editorial (p 15). But we must also accept that there are no certainties in science or medicine. Evaluating evidence and treating patients are both about balancing probabilities not following rules. Guidelines are a tool that must be used with care, not least because they may be out of date. In this study, updates were published one to 15 years after the original (mean 6.7 years). They were longer, contained more recommendations, and cited more evidence. But most of it remained level II (non randomised trials or observational studies) or level III (expert opinion or case studies).
Arch Intern Med 2011;171:18-22

COMPARISON OF FIVE UPDATED GUIDELINES



Adapted from *Arch Intern Med* 2011;171:18-22