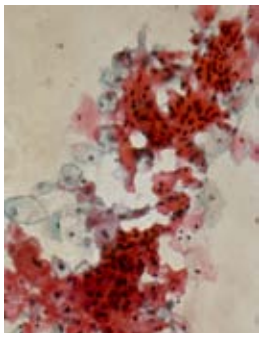
Safe thresholds for hybrid capture 2 test in primary cervical screening

Higher cut offs could be used in some circumstances, but equivocal values should not be ignored



SPL

RESEARCH, p 1191

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Substantial evidence shows that testing for human papillomavirus (HPV) DNA with hybrid capture 2 is more sensitive but less specific than cytology at detecting high grade cervical intraepithelial neoplasia.[1] The sensitivity of hybrid capture 2 relative to cytology depends on the quality of the cytology, but its absolute sensitivity is uniformly high (about 96% overall and >90% in most studies).[2] Its specificity depends on the level of HPV infection in the population. Typically 6-10% of women aged 30-64 will test positive.

For many years studies have looked at whether increasing the threshold for positivity would make the test more useful by trading a small loss in sensitivity for a large reduction in the clinical false positive rate. In the linked systematic review, Rebolj and colleagues assess randomised controlled trials that investigated the effect of different cut-off points on the sensitivity and specificity of the hybrid capture 2 test.[3] The authors suggest that the standard cut off of 1 relative light units/cut off (rlu/co) should be changed to 10 rlu/co.

Although the data show that the loss of sensitivity associated with increasing the cut-off point is small compared with the reduction in the false positive rate, ignoring test results between 1 and 10 rlu/co is questionable. Hybrid capture 2 has been regarded as the gold standard precisely because of its high sensitivity. The negative predictive value of the test is so high that the screening interval can safely be extended to six years or longer.[4] Ironically, the threshold of 10 rlu/co would give hybrid capture 2 similar sensitivity (to HPV DNA) of its predecessor, hybrid capture 1, which was replaced because its clinical sensitivity was considered too poor.[5] Some of the false positive results with hybrid capture 2 are the result of cross-reactivity with low risk HPV types, and this has been removed in several more recent assays, which claim to have a similar clinical sensitivity and a substantially improved specificity.

In practice, the low specificity of hybrid capture 2 is dealt with by using a second test (on the same sample). For instance, cytology has been proposed to triage HPV positive women, with immediate colposcopy for those with mild dyskaryosis or worse and repeat screening at 6-12 months for those with normal cytology or borderline changes.[6] Three subsequent randomised controlled trials using such an algorithm (but referring on any cytological abnormality) found that comparable numbers or even fewer women were referred to colposcopy in the HPV arm than in the cytology arm.[7-9] Similarly, the rlu/co of hybrid capture 2 could be used to manage women selectively. Women with less than 1 rlu/co could be screened at an extended interval (6-10 years), whereas those with ≥1 rlu/co should have cytology performed on the same sample, and women with moderate dyskaryosis or worse should be referred to colposcopy. What happens to the others might depend on both their cytology and their rlu/co value. Those with any cytological abnormality and ≥10 rlu/co could be referred for colposcopy. Those with normal cytology or less than 10 rlu/co could be rescreened after 12-18 months or, for women aged under 35 years, even three years later.

An individual patient meta-analysis (including split sample studies, which are typically more informative than randomised controlled trials for studying cross sectional test performance) is needed to explore the usefulness of such an algorithm. Although it will be unknown how many (if any) of the cases of high grade cervical intraepithelial neoplasia found at baseline would have progressed to cancer (or even regressed) by 18 months, the numbers that might be involved in a "delayed diagnosis" could be quantified. Indeed, in many of the trials reviewed by Rebolj and colleagues, the baseline sensitivity included all disease found within one year (and in one study 30 months) of screening. Any such review should also take into account the collection medium and the sample processing, both of which can affect the occurrence of low level false positive results.

The decision as to what threshold to use with hybrid capture 2 in primary cervical screening comes down to a trade off between false negatives (women missed who will go on to develop invasive cancer before their next screen) and false positives (women referred to colposcopy and potentially made anxious by an HPV infection with no short term risk of cervical cancer). The defensive approach to medicine practised by those wishing to use hybrid capture 2 in Europe or North America means that most will err on the side of caution and stick to the standard threshold.

When hybrid capture 2 is used in addition to cytology, as in the United States, ignoring low level positive results (1.0-10 rlu/co) in women with normal cytology may be appropriate when the quality of cytology is good. However, when hybrid capture 2 is used to triage low grade cytological abnormalities (as it will be in England from the end of 2011), it would not be advisable to ignore a mildly dyskaryotic smear with a positive hybrid capture 2 result, albeit at the level of 8 rlu/co. Similarly, if hybrid capture 2 is used as a test of cure after treatment for cervical disease, it would need to be as sensitive as possible before it could be used to discharge women treated for high grade cervical intraepithelial neoplasia to routine screening.

There is a strong argument for using HPV DNA testing as a primary screen in women over the age of 35. If this is done using hybrid capture 2, women with equivocal results (1.0-10 rlu/co) should be managed less intensively than those with strongly positive results (>10 rlu/co) to reduce the cost and anxiety associated with false positive results, but few people would wish to ignore such results completely.

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Effectiveness of insoles in treating medial osteoarthritis of the knee

Traditional lateral wedged insoles are unlikely to benefit people with mild to moderate disease

RESEARCH, p 1192

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In the linked randomised controlled trial Bennell and colleagues assessed the effect of lateral wedge insoles on the symptoms and progression of medial knee osteoarthritis.[1] They found that such insoles worn for one year provide no symptomatic or structural benefit compared with a flat control insole.

The medial tibiofemoral compartment is most commonly affected in osteoarthritis of the knee, probably because an external adduction moment (the tendency of a force to twist or rotate an object) in the knee during walking causes compression of the medial compartment.[2] Varus knee alignment (bowleg) has been reported as one of the best predictors of a high knee adduction moment during walking, and there is strong evidence that varus alignment or a high adduction moment predicts faster progression of knee osteoarthritis.[3] Lateral wedged insoles and valgus knee braces have therefore been developed as a conservative approach to altering mechanical loading and reducing the symptoms and progression of knee osteoarthritis. Several studies show that lateral wedged insoles reduce the knee adduction moment; this effect seems more pronounced in mild osteoarthritis (early to mild radiographic stage) than in more advanced stages (moderate to severe).[2]

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Lateral wedge insoles are promising in theory but in practice are unlikely to help symptoms

A systematic review of braces and orthoses for knee osteoarthritis included three randomised controlled trials on insoles.[4] One found a significant decrease in the use of non-steroidal anti-inflammatory drugs in people prescribed wedged insoles compared with neutral insoles after six months but found no differences in symptom scores.[5] The second showed that the femorotibial angle was significantly improved in people using elastically strapped wedged insoles rather than traditional wedged insoles at six months and two years; symptom scores were also significantly better in people using strapped insoles at six months.[6] The third trial showed that symptoms were borderline significantly better after six weeks of treatment with a strapped wedged insole compared with a sock-type wedged insole.[7]

Since the systematic review, four other trials on the effect of lateral wedged insoles have been published. A crossover trial compared lateral wedged insoles with neutral insoles for six weeks in patients with mainly severe medial knee osteoarthritis and found that wedged insoles had no significant effect on symptoms.[8] The second trial randomised patients with mild to severe medial osteoarthritis of the knee and varus alignment into five groups treated for 12 weeks with different kinds of neutral and lateral wedged insoles; strapped wedged insoles had the best effect on symptoms, but the authors did not report between group differences.[9] A recent randomised controlled trial showed no difference in scores for pain, function, or stiffness after one month to one year of a lateral wedged insole compared with a neutral insole in people with mild to severe medial knee osteoarthritis.[10] The fourth and most recent randomised controlled trial compared lateral wedged insoles with a valgus brace in patients with mild to moderate medial knee osteoarthritis, and it showed no difference in symptom scores after six months of treatment between the intervention groups.[11]

Bennell and colleagues' trial is the largest trial (n=200) to look at wedged insoles in osteoarthritis of the knee.[1]

Inclusion criteria were medial knee pain during walking in combination with mild to moderate osteoarthritis of the medial knee and a varus knee alignment. In addition to assessing the symptoms at the end of the one year trial, the annual structural change was assessed by magnetic resonance imaging. The daily use of the insoles was within the recommended range; the loss to follow-up was acceptable; and randomisation, blinding, and analyses procedures were adequate. This trial therefore adds important evidence for the lack of clinical effectiveness of a wedged insole in patients with mild to moderate medial knee osteoarthritis. Moreover, it also found no structural benefit. The pragmatic design is one of the strengths of the study because it aims to reflect how the intervention would be used in clinical practice. However, such a design may also result in non-optimal use of the intervention; for example, the participants in this trial were allowed to wear the wedged insole in their own (sometimes high heeled) shoes. In addition, almost 80% of the participants showed joint space narrowing of the lateral knee compartment too, and the increased load at the lateral compartment may have affected this compartment negatively.

In this trial, as in many others, half of the patients already had radiographic evidence of moderate osteoarthritis of the knee, and wedged insoles have the greatest effect on the adduction moment in the knee in early to mild osteoarthritis.[2] Future studies should therefore focus on the effect of wedged insoles, especially elastically strapped ones, in early stage osteoarthritis.

Evidence so far indicates that the use of traditional lateral wedged insoles will on average not benefit patients with mild to moderate medial knee osteoarthritis and cannot be recommended.

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Can a dietary supplement prevent pre-eclampsia?

L-arginine with vitamins show promise, but there are good grounds for caution

RESEARCH, p 1193

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Pre-eclampsia is a pregnancy syndrome that is defined as the gestational onset of hypertension and proteinuria; it affects 2-8% of first time pregnant mothers and has a marked international variation.[1] The highest incidence of maternal mortality as a result of pre-eclampsia is in Latin America and the Caribbean, where it accounts for a quarter of maternal deaths.[2] Most of these maternal deaths are caused by uncontrolled hypertension and multi-organ failure. A simple, cheap, and safe intervention to prevent pre-eclampsia would have a major impact on global health. In the linked randomised trial, Vadillo-Ortega and colleagues assess whether supplementation during pregnancy with L-arginine (the substrate for synthesis of the vasodilatory gas, nitric oxide) and antioxidant vitamins in a medical food reduces pre-eclampsia in a high risk population.[3]

Despite its simple definition, pre-eclampsia is a complex syndrome with multiple causes that can present with a variety of clinical features. For this reason, a single treatment is unlikely to be effective in all women at risk. As our understanding of pre-eclampsia improves, new therapeutic options emerge. Over the past 20 years, low dose aspirin and calcium supplements have had partial success in preventing the development of pre-eclampsia. Other attempts at preventing pre-eclampsia have been disappointing, in particular the use of antioxidant vitamins.[4]

For a healthy pregnancy outcome blood flow must increase to almost all maternal organs, in particular the uterus and placenta. The maternal vasculature dilates in response to increased activity of the endothelial enzyme nitric oxide synthase.[5] This enzyme produces the vasodilator substance nitric oxide after stereospecific oxidation of L-arginine. Until recently, it was thought that L-arginine circulated in such abundance that it could not be a rate limiting factor for endothelial production of nitric oxide. However, women with pre-eclampsia have endothelial damage and raised plasma concentrations of a competitive inhibitor of nitric oxide synthase, asymmetrical dimethyl arginine (ADMA).[6] In vitro, nitric oxide synthase activity is inhibited by intracellular ADMA and rescued by L-arginine supplementation.[7] Therefore, L-arginine supplementation in pregnancy could possibly overcome nitric oxide synthase inhibition, improve maternal endothelial function, and reduce the risk of pre-eclampsia.

In Vadillo-Ortega and colleagues' trial, women at high risk of pre-eclampsia were randomised to three groups: daily food bars containing both L-arginine and antioxidant vitamins; bars containing only vitamins; and bars with neither L-arginine nor vitamins (placebo).[3] The intervention started at around 20 weeks' gestation and continued until delivery. The proportion of women developing pre-eclampsia was 30.2% in the placebo group, 22.5% in the vitamin only group, and 12.7% in the L-arginine plus vitamin group. The risk ratio was 0.74 (95% confidence interval 0.54 to 1.02) when comparing the vitamin only group with the placebo

group and 0.42 (0.28 to 0.62) for the L-arginine plus vitamin group versus the placebo group. L-arginine is a widely available food supplement so the implications of this result could be profound. However, several concerns suggest that a cautious interpretation is warranted.

Firstly, it is not clear how the combination of antioxidant vitamins and L-arginine led to a reduction in pre-eclampsia. Crucially, the effects of L-arginine alone were not studied. A previous trial of L-arginine supplementation for pregnant women with chronic hypertension showed less need for antihypertensive agents, but no reduction in the incidence of superimposed pre-eclampsia.[8] Furthermore, women who go on to develop pre-eclampsia have been found to have higher, not lower, plasma L-arginine concentrations.[9] High L-arginine concentrations may counteract raised ADMA values, but other vasoconstrictor effects may persist in women who are vulnerable to pre-eclampsia.[9] Vadillo-Ortega and colleagues did not measure ADMA concentrations.[3]

Secondly, the primary outcome was classified in a binary manner. The difference in systolic blood pressure between the groups (L-arginine plus vitamins *v* placebo) was 5 mm Hg or less. The large reduction in relative risk was partly driven by a small number of women just crossing the diagnostic blood pressure threshold for pre-eclampsia. Such a simple divide is a poor reflection of the underlying biology: pre-eclampsia is not an "all or nothing" disease, and a more nuanced approach suggests quite modest effects overall.

A third concern relates to the generalisability of the findings to women at lower risk and to other settings. Most of the women in the trial (95%) had a previous pregnancy affected by pre-eclampsia. Even for such a high risk group, the rate of pre-eclampsia in the study population was exceptionally high at 30%, compared with 15% in a similar group in Sweden.[10] Beneficial effects of dietary supplements will generally be most pronounced in people with low levels or deficiency of the food supplement in question. Interestingly, calcium supplements reduce the risk of pre-eclampsia in Latin America but not in North America.[11]

Other aspects of the trial were commendable. Although opaque envelopes are not infallible as a means of concealment, allocation was probably adequately concealed. The study was designed to be blinded, with nothing to suggest that knowledge of the randomised allocation affected ascertainment of the outcome. Outcomes were ascertained for all women randomised, and analysis was on an intention to treat basis. Although non-adherence was common, L-arginine was measured and was higher in woman randomised to supplements.

Although the findings are important, crucial questions remain. What is the mechanism of action of L-arginine and vitamins together; what are the effects (including potential adverse effects) of L-arginine given alone; what are the effects in other settings and populations? This is not the conventional "more research is needed" call. Indeed, a crucial first step before more trials are started would be a rigorous systematic review of the numerous inconsistent strands of evidence relating to L-arginine and its possible effects on pre-eclampsia.

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Patient participation groups

NHS reforms offer new and wide ranging opportunities

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Involvement of patients and the public is meant to be at the heart of the coalition government's health policy. *Liberating the NHS* claims to "strengthen the collective voice of patients and public."[1] Patient participation groups are one way in which the views of patients might be heard more clearly in future. Such groups emerged more than 30 years ago but have been slow to gain hold. In 2007, 41% of practices were reported to have a patient participation group,[2] but the true proportion of active groups is probably lower. Their role has always lacked clarity, but the current NHS reforms in England offer new opportunities for these groups.

Patient participation groups are voluntary and usually based around a general practice.[2] Activities undertaken by these groups come under three broad categories.[3] The first concerns health education—for example, running educational meetings for patients. The second role is that of "critical friend"—giving advice and feedback on services provided by the practice. Thirdly, some groups generate material support for practice developments—for example, through fundraising or providing voluntary services.

Surveys carried out by the National Association of Patient Participation have shown that patient participation groups

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are more common in rural than urban communities. Barriers to establishing a patient participation group include lack of time and a perceived lack of interest from patients.[2] The two most important determinants of success are strong leadership and enthusiasm for the group's work by the members themselves. Other prerequisites of success include support from the practice team, selection of appropriate participants, clarity of purpose, and resourcing. Among many obstacles to progress, perhaps the most important is the difficulty, especially for smaller practices, of sustaining commitment among busy staff and members of the group.

Champions of patient participation groups say they benefit individuals who participate and the practices to which they are affiliated. They also suggest that these groups have the potential to enhance social networks. Social cohesion may be indicative of underlying psychosocial risk factors that are known to be closely associated with health.[4] Community participation in health is at the heart of the World Health Organization's strategy and the Healthy Cities agenda.[5] Patient participation groups provide a means of increasing community engagement on local health matters. Could they play a stronger role in primary care in the future?

Liberating the NHS presages the creation of HealthWatch England, a new independent consumer champion within the Care Quality Commission.[1] Local involvement networks, funded by and accountable to local authorities, are supposed to ensure that the views of patients and carers are integral to local commissioning.[1] Exactly how general practice commissioning consortiums are to be held accountable to the public is unclear. Charities fear that local HealthWatch bodies will not have the resources to ensure that patients have a say in local service development; they will need to be strengthened.[6]

Some patient participation groups already have the experience to contribute to this new agenda. In particular, they could undertake a more formal role in scrutinising practice services. Secondly, they could assist the new commissioning bodies—for example, by helping to assess local healthcare needs and set priorities. Currently, practices are not required to support patient participation groups but new contractual incentives will reward practices "for routinely asking for and acting on the views of their patients."[7] Under the terms of a Directed Enhanced Service, practices can be paid for establishing a "patient reference group," undertaking a local practice survey, and publicising actions taken as a result.

Few patient participation groups are currently equipped for a more formal scrutiny role. Members face conflicts of interest overseeing their personal doctors and local practices. They may not be representative of the communities they serve. They may lack relevant training and expertise to inform commissioning. Sustainability is a central concern; can these groups serve multiple practices?

The government extols the "Big Society," a call for the decentralisation of power and more public involvement in managing local communities.[8] The concept is destined for continuing ridicule at a time of increasing austerity and cuts in public sector spending. However, the themes that underlie the Big Society (and the similarly ill fated "Third Way" that preceded it)—of voluntarism, localism, and transparency—are not without merit.[9] They are consistent with attempts to place greater control in the hands of patients and users. They can be aligned with the core values of mutuality and fairness that are embodied in the NHS. Empowered patients are the best defence against threats to the integrity of the NHS.

Patient participation groups need clear goals, incentives, and resources, and practices now have further guidance on how to establish and sustain them.[7] An expanded role for patient participation groups could provide a means of increasing public involvement in the NHS while offering democratic legitimacy to the commissioning process.

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Direct to consumer genetic testing

Regulations cannot guarantee responsible use; an international industry certificate is needed

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Genetic tests sold on the internet often claim to profile a person's risks for a wide range of diseases, including diabetes, Parkinson's disease, and certain cancers.[1] The DNA sample is usually taken at home by the consumer swabbing her or his cheek and sent to the laboratory by mail. Results may be communicated over the telephone, by post, or electronically. In 2009, the *BMJ* published a clinical review that recommended caution when clinicians are asked to interpret test results in patient consultations.[2] The recent widening of applications and easy access to direct to consumer genetic tests is likely to increase the number of patients who see their doctor because of a test result that indicates increased risk of disease.[3]

Urgent calls for regulation of direct to consumer genetic tests have come from a wide variety of international policy arenas as the industry offering these services expands.[4 5]

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In 2010 the Australian National Health and Medical Research Council published a report on medical genetic testing for health professionals, which acknowledged many problems with direct to consumer tests, but also noted that as market products they cannot be banned.[6] In the United Kingdom, the Human Genetics Commission has published a framework of ethical guidance that tackles informed consent, marketing, risk communication, availability of counselling, and data protection for direct to consumer genetic testing.[7] In the United States, the Food and Drugs Administration has looked into the practices of US based direct to consumer companies, and, at its most recent meeting in March 2011, its advisory committee on molecular and clinical genetics recommended involvement of doctors and that "specific tests should be offered solely on prescription." The problem with these regulatory approaches is enforcement. A globally acting, internet based industry cannot be forced to comply with laws or regulations that are binding only country by country.[8]

The validity and clinical utility of the tests currently available varies greatly.[9] Although results given by some tests may be well founded, other genetic testing products have been described as scientifically meaningless.[5] Many of the tests have not been evaluated clinically.[10] Most genetic variants included in direct to consumer test panels are associated with multifactorial complex conditions of low predictive value.[8 11] Serious criticisms have been made about dubious usage of secondary data without informed consent, as well as the lack of professional advice on how to interpret the genetic test outcomes and how to integrate them meaningfully into daily life and the image of the past and future self.[5 12]

However, it would be unhelpful to dismiss these tests out of hand, because consumers will continue to use them and they can help to identify some risk factors, particularly monogenetic variations. In some cases the tests have alerted patients and doctors to certain conditions. In a US study from 2010, 133 specialists in clinical genetics reported on patients who came to them as a consequence of direct to consumer genetic testing, either self referred or physician referred. Over half of the professionals judged the tests as potentially clinically useful, in particular tests for *BRCA1* and *BCRA2* (87%), which were far ahead of all other genetic tests (37%).[3]

Clear criteria are needed for health professionals and consumers to identify clinically useful tests of good ethical standard. Quality assurance of direct to consumer testing requires a type of rigorous control of these genetic tests that is not bound to national laws or regulations. An international product quality certificate that controls for compliance with ethical standards, provisions for counselling, and stringent standards of scientific validity could fulfil this task. Obtaining such a product quality certificate would be voluntary, yet should bring market advantages. International Standards Organisation (ISO) certificates, for example, are well established instruments for product quality. A similar modus of standard setting for direct to consumer genetic tests would benefit consumers and the health sector.

The availability of certified products would enable consumers to choose tests that they know meet high scientific and high ethical standards. An ISO-type quality assurance certificate should present a clear market advantage for the companies holding it.

However, product accreditation would not solve all the problems arising from the development of direct to consumer genetic tests. The coexistence of a second tier market of uncertified products of low quality cannot be prevented, and products and practices that are outlawed in some countries—such as genetic testing for prenatal sex selection or secret paternity tests—may boom in this second tier market. Yet, for healthcare professionals an easy system of recognising uncertified genetic testing products would render low quality tests a marginal problem. The certification would present a viable method to decide whether the test a patient used can be taken seriously. Such practice in the medical sector would align with the practice in judicial and forensic systems of only accepting genetic test results from certified laboratories, but it would also exceed their local limitation by using a globally recognised identifier for quality.

Ultimately, the means to discipline the use of genetic testing within the bounds of respect for human rights, especially of individual and group self determination, can only come from a global debate on values and rights. Regulations, laws, and certificates cannot guarantee responsible use, and thus a quality certificate for direct to consumer products seems the most helpful instrument, in lieu of such political debates.

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- Feature: Direct to consumer genetic testing (*BMJ* 2008;336:858)
- News: Commission aggress framework to regulate genetic tests sold direct to consumers (*BMJ* 2010;340:c2752)
- Observations: Beware the fortune tellers peddling genetic tests (*BMJ* 2011;342:c7233)

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