Oxford Primary Care 2015

Cutting-edge research in the consulting room

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In partnership with:
National Institute for Health Research
Clinical Research Network
Thames Valley and South Midlands
Rapid Diagnostic Tests

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Director: Diagnostic Horizon Scan Programme

18 May 2015
Stomach cancer
By Michelle Roberts
Health editor, BBC News online

A quick and simple breath test diagnose stomach cancer, study reveal.

Scientists from Israel and China for the first time accurately detecting and distinguishing cancers from other complaints in 180 patients.

The British Journal of Cancer says could revolutionise and speed up cancer diagnosis.

About 7,000 UK people develop to have an advanced stage of the dises.

Two-fifths of patients survive for at alive after five years, despite treatment.

Currently doctors diagnose stomach cancer patients using a probe and a scan.

The new test looks for chemical in to patients with stomach cancer.

Volatile organic compounds
Cancer appears to give off a signal that can be detected, and perhaps even detected.

The science behind the test itself is in the possibility of the

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17 January 2013 Last updated at 12:19

Phone apps may delay skin cancer diagnosis

Using a smartphone app to decide whether a mole is cancerous could delay sometimes life-saving treatment, according to American researchers.

The University of Pittsburgh scientists put four applications to the test by showing them 198 pictures of cancers and less concerning skin conditions.

Three of the apps wrongly labelled the cancerous lesions as unproblematic in almost a third of cases.

Doctors warn using phones rather than seeking expert help could be harmful.

The research, published in the Journal of the American Academy of Dermatology, looked at four commonly used applications.

The images selected to test the apps were all of skin lesions that were later removed and checked for an accurate diagnosis.

Three of the apps analysed the pictures using automated algorithms, without the involvement of doctors.

But users submitting pictures to the fourth app had their images reviewed by a qualified skin specialist.

In this case only one out of 53 cancerous lesions was misdiagnosed, but this app cost $5 (£3.10) per use.

Prof Laura Ferris, lead researcher of the study said, “It is important that..."
What’s out there?

- Literature
- Meetings with Industry
- Ask clinicians
Horizon scanning reports

The Oxford Diagnostic Horizon Scan Programme identifies new and emerging diagnostic technologies relevant to primary care in the NHS.

The horizon scanning reports summarise why the technology is important, provide an overview of the current available evidence and assess whether it could be adopted in the NHS and if so, what the requirements are for the delivery of the technology into practice.

These reports are freely accessible and disseminated to the NIHR Health Technology Assessment Programme (HTA), the National Institute for Health and Clinical Excellence (NICE) and commissioners of health care services to facilitate adoption and identify further research requirements.

We are funded by the National Institute for Health Research (NIHR) and collaborate with the Health Economics Research Centre at Oxford University.

Find out more about our research

www.oxford.dec.nihr.ac.uk/horizon-scanning
What is the evidence?

• Is it accurate (enough)?
• Is it feasible and who would use it?
  e.g. GP, nurse, patient…
• Will it change practice? e.g. Does it help decision making, reduce referrals, etc.?
• How do patients/doctors feel about using it?
• Is it cost effective?
Self-monitoring of INR

✅ Accuracy:
Systematic review of the accuracy of 3 commonly available point-of-care coagulometers: accuracy is comparable to laboratory measures and adequate for clinical use

✅ Clinical impact:
Systematic reviews including individual patient data analyses (over 5000 patients)
- Self-management (i.e. self-testing and self-adjusting warfarin) – reduces thromboembolic events (RR = 0.47) and all-cause mortality (RR = 0.55) but no effect on major bleeds

- Self-monitoring (i.e. self-testing and warfarin adjustment by clinician) – significant reduction in thromboembolic events (HR = 0.51), but not for major bleeds or death

✅ Patient acceptability:
UK trials suggest 24% of patients would agree to carry out self-monitoring, of which 70% could be successfully trained and would be able to do so
What do the guidelines say?

The 2014 NICE guideline on self-monitoring coagulation status (DG14):

“In patients with AF who require long-term anticoagulation, self-monitoring should be considered if preferred by the patient and the following criteria are met:

- **the patient** is both physically and cognitively able to perform the self-monitoring test, or in those cases where the patient is not physically or cognitively able to perform self-monitoring, a designated carer is able to do so
- **an adequate supportive educational programme** is in place to train patients and/or carers
- **the patient’s ability to self-manage** is regularly reviewed
- **the equipment for self-monitoring** is regularly checked via a quality control programme.”
What is currently happening?

Recent data from the Churchill Hospital in Oxford:
160 “self-testers” (out of about 8,500 patients) but none who self-manage
D. Keeling, personal communication

Bottom line?

- Patients who self-monitor or self-manage can improve the quality of their warfarin therapy
- Self-monitoring reduces the rate of clot-related events and is a safe option for suitable patients of all ages
- Patients should be offered the option to self-manage, with health-care support as back-up
Point-of-care tests for coeliac disease

Biotech Biocard Celiac Test
5351095
£20.42

Collect in store
Home delivery

Quantity 1

Add
Check store availability

Biotech Biocard Celiac Test is a rapid and reliable home test for the detection of celiac disease from a fingertip blood sample. Celiac disease is an intolerance to gluten.
Accuracy:
- 5 case-control studies in biopsy-confirmed coeliac disease patients and lab controls
- Sensitivity 90%-97% and specificity 79%-100%
- No studies in primary care

Clinical impact:
- Accuracy may be overestimated due to study design and selective populations
- Sensitivity in asymptomatic children was much lower (65-79%) – ability to rule out coeliac disease in children is reduced
- ~8% of coeliac disease patients are IgA deficient, test may give a false negative result
- Patients self-testing may begin gluten-free diets without confirmation testing or additional advice (and investigations for potential comorbid conditions)

Patient acceptability:
- No research evidence
- Comments suggest they like the rapid and immediate result but some do have reservations regarding the accuracy
The evidence for point-of-care tests is limited
In the future they may be helpful in the diagnostic work-up of coeliac disease in primary care settings by increasing speed of results or access to testing in some settings, as sensitivity and specificity are comparable with laboratory-based serology. However, a negative result does not safely rule out coeliac disease.
Autoimmune markers for the diagnosis of rheumatoid arthritis

✅ **Accuracy:**
Meta-analysis of the diagnostic accuracy of rheumatoid factor (50 studies) and anti-cyclic citrullinated peptide antibody (37 studies):
- RF: sensitivity 69%, specificity 85%
- ACPA: sensitivity 67%, specificity 95%
- Setting: Hospital arthritis clinics, no large studies based in primary care

✅ **Clinical impact:**
- 60–70% patients with RA have a positive RF, which is predictive of disease severity, but not useful for diagnosis
- Only 11–20% of people with musculoskeletal symptoms and a positive RF actually have RA
- Unclear whether adding ACPA to RF provides any added benefit
- No evidence to support use of RF or ACPA as diagnostic tests for RA in primary care
What do the guidelines say?

The 2009 NICE guideline on rheumatoid arthritis (CG79):

- “Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:
  - the small joints of the hands or feet are affected
  - more than one joint is affected
  - there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

- Refer urgently any person with suspected persistent synovitis of undetermined cause, even if their blood tests show a normal acute-phase response or negative rheumatoid factor.”
What is currently happening?

Cohort study and retrospective analysis of RF requests made to hospital immunology lab between 2003 and 2009:

- 67% of requests were from primary care
- Substantial variation between practices


Bottom line?

- Role of RF in diagnosing RA in primary care remains unclear
- Newer tests (e.g. ACPA), are emerging with higher specificity and positive predictive values, but similar sensitivity
- Currently GPs should base diagnostic and referral decisions on clinical features. A positive RF or ACPA has value in supporting these decisions, but a negative test does not rule out disease
What is the ONE thing I need to remember from today?

Don’t believe everything you are told, Ask for the Evidence!
If you come across a new test or are thinking about implementation:

Have a look at our website
http://www.oxford.dec.nihr.ac.uk/

If we haven’t assessed it, please let us know about it!
dec@phc.ox.ac.uk
Point-of-care tests in airways disease

Dr Helen Ashdown. 18 May 2015
GP and NIHR Doctoral Research Fellow
Outline

• Eosinophils, FeNO and steroid responsiveness in asthma and COPD
• Immediate horizons: FeNO in asthma
• More distant horizons: Eosinophils in COPD
• Primary care studies on the horizon
Airways disease

- Inflammation and bronchoconstriction
- $T_{H2}$-mediated
  - Eosinophils
  - Nitric oxide

- NO and eosinophils increased in airway
- Steroid treatment targets this \( T_H^2 \) response
Steroid responsiveness

- Eosinophilic airway inflammation (NO, sputum and blood eosinophils) is a reliable predictor of response to steroids, regardless of underlying diagnostic label.

- Management strategies which seek to minimize eosinophilic airway inflammation substantially reduce exacerbation frequency in asthma and COPD.

Over-diagnosis of asthma

• Non-specific symptoms – GORD, post-viral bronchial hyper-responsiveness, anxiety

• Trials of inhaled steroid treatment likely to be positive
  • Self-limiting
  • Fluctuation over time
  • Observer bias

Immediate horizons: FeNO

- Portable easy-to-use breath test
- FeNO correlates with airway eosinophilic inflammation
- Reliably predicts response to steroids

NICE

- Add-on test to diagnostic pathway
- Sensitivity ~80%, specificity ~90% (FeNO cut-off 40ppb vs. physician)
- £10-13 per use (£6.36 equipment cost)
From diagnostic algorithm A: adults and young people older than 16 with obstructive spirometry (FEV₁/FVC ratio less than 70%)

Offer a bronchodilator reversibility (BDR) test. Regard an improvement in FEV₁ of 12% or more, together with an increase in volume of 200 ml or more, as a positive test.

- **-ve BDR**
  - Offer a FeNO test. Regard a FeNO level of 40 ppb or more as a positive test.
  - If the FeNO level is less than 25 ppb, consider monitoring peak flow variability for 2-4 weeks. Regard a value of more than 20% variability as a positive test.
  - If the FeNO level is between 25 and 39 ppb, consider monitoring peak flow variability for 2-4 weeks. Regard a value of more than 20% variability as a positive test.
  - Consider a direct bronchial challenge test with histamine or methacholine. Regard a PC20 value of 8 mg/ml or less as a positive test.

- **+ve BDR**
  - Offer a FeNO test. Regard a FeNO level of 40 ppb or more as a positive test.
  - If the FeNO level is less than 25 ppb and there are ongoing symptoms, consider a direct bronchial challenge test with histamine or methacholine. Regard a PC20 value of 8 mg/ml or less as a positive test.

**Suspect asthma**

Do not rule out other diagnoses if symptom control remains poor after treatment.

**Review the diagnosis**

- after 6-10 weeks repeat spirometry and objective measures of asthma control and review symptoms

**Consider**

- alternative diagnoses or referral for specialist opinion

**Consider alternative diagnoses**

**Diagnose with asthma**

Do not offer as diagnostic tests:
- skin prick tests to aeroallergens
- serum total and specific IgE
- peripheral blood eosinophil count
- exercise challenge.

**Monitor peak flow variability for 2-4 weeks. Regard a value of more than 20% variability as a positive test.**

**Consider alternative diagnoses**

**Diagnose with asthma**
DRAFT FOR CONSULTATION (January 2015)
Diagnosis algorithm B2 – objective tests for adults and young people older than 16 with normal spirometry

From diagnostic algorithm A: adults and young people older than 16 with normal spirometry (FEV1/FVC ratio 70% or more)

Offer a FeNO test. Regard a FeNO level of 40 ppb or more as a positive test.

- FeNO
  - FeNO

Monitor peak flow variability for 2-4 weeks. Regard a value of more than 20% variability as a positive test.

- PEFR PEFR
  - PEFR

Offer a direct bronchial challenge test with histamine or methacholine. Regard a PC20 value of 8 mg/ml or less as a positive test.

- BCT BCT
  - BCT

Consider alternative diagnoses

Diagnose with asthma

Do not offer as diagnostic tests:
- skin prick test to aeroallergens
- serum total and specific IgE
- peripheral blood eosinophil count
- exercise challenge.

Distant horizons: COPD

- Inhaled steroid treatment in asthma well-established
- Less consistent benefit in COPD

Eosinophil subgroup in COPD

- $T_H^2$/eosinophil-predominant subgroup of COPD patients – blood and sputum
- May account for inconsistent response to steroids

COPD exacerbations

• RCT of eosinophil-directed vs. standard therapy with oral prednisolone
  • Blood eosinophils ≤ or > 2%
  • Patients who were eosinophil-negative
    • More treatment failures when given steroids
    • Improved symptom scores when given placebo

Long-term COPD

- Steroid treatment improved symptoms, lung function and quality of life scores in more ‘eosinophilic’ patients (sputum)

- Reduction in exacerbations when managed by sputum eosinophil count (Siva 2007)

Future questions

• Translating secondary care research into primary care setting – earlier disease/steroid-naive

• POC blood eosinophils in exacerbations

• Long-term management in steroid-naïve patients
  • Blood eosinophils
  • FeNO
Coming soon to Thames Valley…

• COPD exacerbations
  • RCT of point-of-care eosinophils and CRP to target antibiotics/steroids
  • RCT of point-of-care CRP testing to target antibiotic prescribing (PACE)
• Long-term COPD management
  • Establishing variability of FeNO and blood eosinophils in stable steroid-naïve patients