Oncology

Mammography screening for breast cancer

Ten years ago, a review by the World Health Organization (WHO) estimated mammography screening may reduce breast cancer mortality by around 25%. However, advances in treatment has now led experts to question the value of screening.

A Norwegian prospective study investigated the effectiveness of contemporary mammography screening on breast cancer mortality among women aged 50-79 years. The authors analysed the mortality rates of women invited to screening during implementation of the programme in comparison to those not invited.

During 15,193,034 person-years of observation, 1175 women died from breast cancer in the invited group compared with 8996 who were not invited to screening. After adjustment for confounding factors the mortality rate associated with being invited to mammography screening ratio was calculated at 0.72. To prevent one death, it was estimated that a total of 368 women would need to be invited to screening.

Invitation to modern mammography screening may reduce deaths from breast cancer by around 28%.

Weedon-Fekjaer H, Romundstad P, Vatten J. Modern mammography screening and breast cancer mortality: population study. *BMJ.* 2014; 348:3701.

Adjuvant exemestane in premenopausal breast cancer

Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen in post-menopausal women with hormone-receptor positive early breast cancer. A recent study investigated whether disease-free survival was greater among women receiving ovarian suppression, together with either tamoxifen (n=2358) or the aromatase inhibitor, exemestane (n=2359).

Although overall survival did not differ between the two groups, disease-free survival at five years was greater in the exemestane group (91.1%), compared with tamoxifen group (87.3%), yielding a significant hazard ratio (HR) of 0.72. The rate of freedom from breast cancer at five years was also significantly greater in the exemestane group (92.8% versus 88.8%). The rate of adverse events were similar between the two groups.

Ovarian suppression with exemestane compared with tamoxifen reduces the risk of recurrence.

Pagani O, Regan M, Walley B, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *NEJM.* 2014; 371:107–18.

Sorafenib treatment for thyroid cancer

Differentiated thyroid cancer can be effectively managed by surgical intervention, radioactive iodine administration, or L-thyroxine therapy. However, many patients with locally advanced or metastatic differentiated thyroid cancers become refractory to radioactive iodine. These patients have a poor prognosis due to a lack of efficacious treatment options.

A recent placebo-controlled trial investigated the effect of sorafenib, an oral kinase inhibitor, on progression-free survival amongst 417 with patients radioactive iodine-refractory thyroid cancer. Median progression-free survival was significantly longer in the sorafenib group (10.8 months) compared with 5.8 months in the placebo group (significant HR, 0.59). This was true for all clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of the 207 patients receiving sorafenib, with the most common being hand-foot skin reaction, diarrhoea, alopecia, and rash or desquamation.

Sorafenib significantly improved progression-free survival in patients with locally advanced or metastatic differentiated thyroid cancers.

Brose M, Nutting C, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet.* 2014; 384:319–28.

Rheumatology

Stem cell transplantation for diffuse systemic sclerosis

Systemic sclerosis is an autoimmune connective tissue disease characterised by vasculopathy, autoantibody formation, and fibrosis. Management commonly involves cyclophosphamide, but new research has indicated that autologous haematopoietic stem cell transplant (HSCT) may be a viable alternative therapy.

A recent multicentre trial randomised patients with early diffuse cutaneous systemic sclerosis to receive either HSCT (n=79), or 12 successive monthly intravenous pulses of cyclophosphamide (n=77). The primary endpoint measured event-free survival (defined as death, or persistent major organ failure).

During a median follow up of 5.8 years, 22 events occurred in the HSCT group (19 deaths) and 31 in the cyclophosphamide group (23 deaths). During the first year, more events were recorded in the HSCT group compared with the control group, however, in the long term HSCT exhibited a significantly greater long-term event-free survival benefit (four year HR, 0.29).

Despite an increased treatment related mortality in the first year, HSCT conferred a long-term event-free survival benefit.

Van Laar J, Farge D, Sont J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA.* 2014; 311:2490–8

Hydroxychloroquine for primary Sjögren syndrome

Primary Sjögren syndrome is a systemic autoimmune condition characterised by mouth and eye dryness, pain, and fatigue. Hydroxychloroquine is the most commonly prescribed immunosuppressant for the syndrome, despite limited evidence supporting its efficacy.

To investigate its efficacy, a three year trial consisting of 120 patients were randomly assigned 1:1 to receive either hydroxychloroquine (400 mg/d) or a placebo for a duration of 24 weeks. The primary endpoint measured the number of patients reporting 30% or greater reduction in scores on two out of three numeric scales measuring dryness, pain, and fatigue.

At 24 weeks, 17.9% of patients in the hydroxychloroquine group reached the primary endpoint compared with 17.2% in the placebo – an insignificant difference. Two serious adverse events were recorded by week 24 in the hydroxychloroquine group compared with three in the placebo group.

During the 24 week trial period, hydroxychloroquine did not improve symptoms.

Gottenberg J, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomised clinical trial. *JAMA.* 2014; 312:249–58.

Tofacitinib for rheumatoid arthritis

Methotrexate is currently the first-line treatment for rheumatoid arthritis, but there are considerable concerns about its safety and side effect profile. A recent trial assessed the efficacy of the biologic disease-modifying antirheumatic drug, tofacitinib (a JAK inhibitor), in comparison with methotrexate for patients with active rheumatoid arthritis.

A total of 958 patients were assigned to receive either 5mg or 10mg of tofacitinib or methotrexate over 10 weeks. Two scoring systems measuring structural joint damage (Sharp score) and the proportion of patients that had an ACR score ≥70 (measuring joint pain and swelling) were used as endpoints.

The primary endpoint was achieved in significantly more patients in both doses of tofacitinib compared with the methotrexate group. However, herpes zoster infections were more common in the tofacitinib group (4.0% vs 1.1%) as were confirmed cases of cancer (5 vs 1).

Tofacitinib is superior to methotrexate at reducing signs and symptoms of rheumatoid arthritis, but concerns exist over its safety and side effects.

Lee E, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *NEJM.* 2014; 370:2377–86.

Musculoskeletal

Epidural glucocorticoid injections for spinal stenosis

Lumbar spinal stenosis is caused by narrowing of the spinal canal resulting nerve root compression and in turn, pain, paraesthesia, and weakness. Glucocorticoid injections are widely used to treat the disability, despite limited evidence for its effectiveness and safety.

A North American randomised trial evaluated the effect of either glucocorticoid plus lignocaine injections or lignocaine injections alone. All 400 patients received either one or two epidural injections before the primary outcome was evaluated. It measured the score changes on a disability questionnaire (higher scores indicate greater physical disability).

At six weeks, although scores in both groups had reduced, there were no significant between-group differences in the disability scores. Further, no significant differences were found according to type of injection (interlaminar vs. transforaminal).

Epidural injections of glucocorticoids, plus lignocaine offered no minimal or short-term benefit as compared with lignocaine alone.

Friedly J, Comstock B, Turner J, et al. A randomised trial of epidural glucocorticoid injections for spinal stenosis. *NEJM.* 2014; 371:11–21.

Anaesthesia during hip fracture surgery

Hip fractures are serious injuries that carries as significant risk of mortality and morbidity with 4-10% of patients dying within 30 days of hospital admission. It has been hypothesised that anaesthesia type may influence mortality rate, therefore, a recent retrospective cohort analysis investigated the in-hospital all-cause mortality among patients receiving different types of anaesthesia. A total of 73 284 patients undergoing hip fracture surgery were investigated, of which 84% underwent general anaesthetic, 9.5% recieved regional anaesthesia, whilst 6.5% had combined anaesthesia.

In-hospital deaths occurred in 2.2% of patients undergoing general anaesthesia, 2.1% and 2.4% of those patients receiving regional and combined anaesthesia, respectively. Further analysis calculated the risk for regional anaesthesia was 0.91 when compared with general anaesthesia, and 0.98 for combined.

Hip fracture surgery mortality did not significantly differ between anaesthesia types.

Patorno E, Neuman M, Schneeweiss S, et al. Comparative safety of anesthetic type for hip fracture surgery in adults: retrospective cohort study. *BMJ.* 2014; 348:4022.

Treatment for intra-articular fractures of the calcaneus

Many calcaneal fractures are severe high-energy fractures and often result in prolonged recovery and poor outcomes. To date, there is no consensus as to whether operative management involving open reduction and internal fixation provides better outcomes than the non-operative management utilising splints, elevation, ice application, and early mobilisation.

A recent randomised trial compared the pain and function scores in patients receiving either operative or conservative management post-injury. A total of 151 patients with closed, displaced, intra-articular calcaneal fractures were randomised in a 1:1 ratio between the two groups. Results showed that although pain and function had improved in both groups by 24 months, no significant difference was noted between the two groups. However, both complication and reoperation rates were higher in the operative care group (odds ratio (OR), 7.5).

No symptomatic or functional advantage was observed after surgical management of calcaneal intra-articular fractures of the calcaneus.

Griffin D, Parsons N, Shaw E, et al. Operative versus non-operative treatment for closed, displaced, intra-articular fractures of the calcaneus: randomised controlled trial. *BMJ.* 2014; 349:4483.

Obs & Gyn

The effect of gravity on placental transfusion volume

Delayed cord clamping allows for the passage of blood from the placenta to the baby, and reduces the risk of iron deficiency in infancy. Recommendations advise holding the infant at the level of the vagina for one minute to allow gravity to increase the transfusion volume. However, this process can interfere with the immediate contact of the infant with the mother and may cause low compliance.

A randomised trial assessed the effect of gravity on the placental transfusion volume by comparing the difference in weight before and after cord clamping between those babies held at the level of the vagina (introitus group) versus those held to the mother's chest (abdomen group) during the two minutes following birth. Primary analysis included 197 babies in the introitus group and 194 in the abdomen group. The mean weight gain in the introitus group was 56g versus 53g in the abdomen group - a non-significant difference.

The position of the baby before cord clamping does not affect the placental transfusion volume.

Vain N, Satragno D, Gorenstein A, et al. Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial. *Lancet.* 2014; 384:235–40.

Preconception aspirin and pregnancy

Pregnancy loss is estimated to occur in up to 30% of conceptions. However, some studies have indicated that administration of low-dose aspirin post-conception may positively affect pregnancy outcomes, but there is limited evidence supporting this. Yet the effect of preconception use of low-dose aspirin for pregnancy outcomes has not yet been assessed.

A multicentre trial recruited 1228 women (aged 18-40) with a history of pregnancy loss. They were then randomised to receive either 81mg of aspirin daily or a placebo, in addition to folic acid for up to six menstrual cycles or 36 weeks gestation. The primary outcome assessed the livebirth rate.

Of the 535 women in the aspirin group, 58% had livebirths compared with 53% in the placebo group, which resulted in a non-significant difference in livebirth rate of 5.09%. Both adverse events and pregnancy loss rate did not differ between the two groups.

Preconception low-dose aspirin is

not recommended for the prevention of pregnancy loss.
Schisterman E, Silver R, Lesher L, et al. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet.* 2014; 384:29–36.

Interpregnancy interval and birth outcomes

The time interval between pregnancies is considered an important and modifiable risk factor for adverse birth outcomes. Typically, short intervals (<18 months between birth and conception), and long intervals (>23 months) have a higher risk of preterm birth, small for gestational age birth, and low birth weight. However, much of the previous research does not adjust for confounding factors such as genetic predispositions, and socioeconomic status.
A recent retrospective cohort study examined the effect of interpregnancy intervals on the incidence of adverse pregnancy outcomes among 40 441 mothers. The study also adjusted for maternal confounding factors.

After adjustment for confounding factors, the risk involved with short interpregnancy intervals were more modest than previously estimated. The adjusted OR for short interpregnancy intervals (0-5months) was 1.07 for preterm birth, 1.03 for low birth weight, and 1.08 for small for gestational age. However, adjusted OR still showed a persistent high risk of small for gestational age and low birth-weight for long interpregnancy intervals.
Ball S, Pereira G, Jacoby P, et al. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ.* 2014; 349:4333.

Letrozole for infertility in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility. Current first-line treatment for infertility among these women involves treatment cycles of clomiphene; however, it has poor efficacy and a relatively high multiple pregnancy rate. Aromatase inhibitors, including letrozole, may provide better outcomes.

To compare the two treatments a randomised trial assigned women to receive either letrozole (n=374) or clomiphene (n=376) for up to five treatment cycles. The primary outcome measured live-births during the treatment period.

Women receiving letrozole had significantly more cumulative live-births than those receiving clomiphene (25.5% vs. 19.1%; rate ratio for live-birth, 1.44) without any significant differences in overall congenital abnormalities. Cumulative ovulations was also significantly higher in the letrozole group than with clomiphene (61.7% vs. 48.3%). No significant inter-group differences were observed for pregnancy loss or twin pregnancy.

Higher live-birth rates were achieved with letrozole compared with clomiphene.
Legro R, Brzyski R, Diamond M, et al. Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome. *NEJM.* 2014; 371:119–29.

CPD Challenge

See page 53 to test yourself on this article

Pain Management

Telecare for management of chronic pain

Chronic musculoskeletal pain is the most common symptom reported in primary care. Despite this, few clinical trials investigating interventions enhancing pain management have been published, or the optimisation of analgesic therapy.

The SCOPE randomised trial assessed the effectiveness of a telecare intervention for chronic pain versus usual care in 250 patients with chronic musculoskeletal pain. The intervention group received 12 months of telecare management, coupling an automated symptom monitoring with, and algorithm-guided approach to optimising analgesic.
The usual care group received all care from their primary care physicians. The primary outcome measured self-reported pain scores (0-10; higher scores signify more pain).

Pain scores showed a significant one point reduction in pain score in the telecare group compared with the usual care group. Patients in the intervention group were also more likely to show >30% improvement in pain scores.

Telecare management increased the proportion of patients with improved chronic musculoskeletal pain.
Kroenke, K, Krebs, E, Wu, J, and Yu Z. Telecare collaborative management of chronic pain in primary care: A randomised clinical trial. *JAMA.* 2014; 312:240–8.

Naloxegol for opioid-induced constipation

Between 40% - 90% of patients taking opioids suffer from constipation or other debilitating gastrointestinal side effects. Recently, a new drug, naloxegol (an oral, peripherally acting μ-opioid receptor antagonist) has been assessed for its efficacy against opioid-induced constipation in two identical randomised trials.

A total of 1352 were assigned to receive either a daily dose of 12.5 or 25mg of naloxegel or placebo. The primary outcome measured the 12-week response rate, which was defined as ≥3 spontaneous bowel movements per week and an increase of ≥1 spontaneous movements over the trial period.

Response rates were significantly higher with 25mg of naloxegol than with placebo (intention to treat population: 44% versus 29%; and in patients who had an inadequate response to laxatives: 49% versus 29%). Response rates were also significantly higher than placebo for those patients receiving 12.5mg of naloxegol.

Naloxegol resulted in a reduction of opioid-induced constipation without reducing the analgesic effects.
Chey W, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *NEJM.* 2014; 370:2387–96.

HIV/AIDS

Dolutegravir for HIV-1 infection

Boosted protease inhibitor regimens are often preferred as first-line therapy for treatment-naïve patients with HIV/AIDS. However, dolutegravir is an integrase inhibitor that can be taken once daily without pharmacokinetic boosters, and boasts a reduced profile for drug interactions. A recent non-inferiority trial assessed the efficacy of dolutegravir versus a guideline-recommended boosted protease inhibitor-based regimen.

A total of 484 treatment-naïve patients were randomised to receive either dolutegravir 50mg once daily or darunavir 800mg plus ritonavir 100mg once daily. The primary endpoint was the proportion of patients with HIV-1 RNA concentration lower than 50 copies per mL by week 48.

After 48 weeks, 90% of the patients receiving dolutegravir has reached the primary endpoint versus 83% in the darunavir-ritonavir group. Analysis revealed that dolutegravir is not only non-inferior, but also superior to darunavir-ritonavir treatment. No treatment-emergent resistance was recorded, but two patients in each group had confirmed virological failure.

Once-daily dolutegravir is superior to once daily darunavir plus ritonavir.
Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO):

48 week results from the randomised open-label phase 3b study. *Lancet.* 2014;383:2222–31.

Antiretroviral therapy initiation after HIV self-testing

Achieving a high coverage of HIV testing is a major challenge, but self-testing can overcome some barriers to conventional facility- or community-based testing. However, no research has investigated the initiation of HIV care after self-testing. In the present study, the authors investigated whether offering optional home initiation of HIV care increases the demand for antiretroviral therapy (ART).

A total of 16 600 Malawian residents from 14 clusters nationwide received self-testing kit and were then allocated to facility-based, or optional home initiation of HIV care for those with positive results. The primary outcome measured proportion of adults initiating ART. After six months, a significantly greater proportion of those in the home group than in the facility group had initiated ART (2.2% vs 0.7%; risk ratio 2.94). Further, significantly more adults reported positive tests in the home group.

Offering home initiation of HIV care rather than standard care increases the proportion of adults initiating HIV care.

MacPherson P, Lalloo D, Webb E, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: A randomized clinical trial. *JAMA.* 2014; 312:372–9.

Implementations of HIV interventions

Epidemiological data shows substantial variation in the risk of HIV infections between communities within African countries. A recently paper hypothesised by focussing on interventions of key populations at high risk of HIV infections could improve the effect of investments in the HIV response.

Using Kenyan data, the authors investigated the potential gains in the efficiency and effectiveness of investments focussed on the people and places at highest risk, rather than a uniform, national approach.

Results established that a uniformly distributed combination of HIV prevention interventions could reduce the total number of new HIV infections by 40% during a 15-year period. With no additional spending, this effect could be increased by 14% during the 15 years - almost 100 000 extra infections, and result in 33% fewer new HIV infections occurring every year by the end of the period if the focused approach is used to tailor resource allocation to reflect patterns in local epidemiology.

The focused approach achieves greater effect than the uniform approach despite exactly the same investment.

Anderson S, Cherutich P, Kilonzo N, et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. *Lancet.* 2014; 384:249–56.

Misc

Recombinant phenylalanine ammonia lyase for phenylketonuria

Phenylketonuria is an inherited disease caused by a deficiency of the enzyme phenylalanine hydroxylase. A recent trial assessed the safety and efficacy of phenylalanine ammonia lyase, an enzyme conjugated with polyethylene (rAvPAL-PEG) given to sufferers as a method of reducing phenylalanine concentrations which, when raised can cause neurocognitive dysfunction.

A total of 25 patients were randomised to receive subcutaneous injections of rAvPAL-PEG at escalating doses in order to assess the safety and tolerability of rAvPAL-PEG. The treatment was effective in all patients at the highest dose, reducing the phenylalanine concentration by over 50%. The lowest phenylalanine concentrations were observed six days post-injection, and were near-baseline by day 21. Adverse reactions included injection-site reactions and dizziness, while 60% of patients receiving a high rAvPAL-PEG dose developed generalised skin rashes.

Higher doses of rAvPAL-PEG reduce phenylalanine blood concentrations while remaining fairly safe and were well tolerated.

Longo N, Harding C, Burton B, et al. Single-dose, subcutaneous recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol in adult patients with phenylketonuria: an open-label, multicentre, phase 1 dose-escalation trial. *Lancet.* 2014; 384:37–44.

Familial risk of cerebral palsy

Cerebral palsy is the most common cause of physical disability in children resulting from damage to the immature brain. However, the causes of the disability remain largely elusive, and whilst many studies have identified risk-factors during pregnancy and the perinatal period, few have investigated the heritable component of cerebral palsy.

A recent cohort study investigated the risks of recurrence of cerebral palsy in family members. Analysis of Norwegian national records estimated if one twin had cerebral palsy, the relative risk of recurrence was 15.6 in the other twin. In families with an affected singleton child, the risk was increased 9.2-fold in the subsequent full sibling, while affected parents were also at increased risk of having an affected child (6.5-fold). After exclusion of preterm births (a strong risk factor for cerebral palsy), familial risks remained and were often stronger.

People born into families in which someone already has cerebral palsy are themselves at elevated risk.

Tollanes M, Wilcox A, Lie R, et al. Familial risk of cerebral palsy: population based cohort study. *BMJ.* 2014; 349:4294.

New treatments for acute bacterial skin infections

Acute bacterial skin infections are a common cause of hospitalisation. Frequent causative pathogens for skin infections include *Staphylococcus aureus*, streptococci and methicillin-resistant Staphylococcus aureus (MRSA), which poses significant treatment challenges. Recently, two new antibiotic agents, oritavancin and dalbavancin, have been trialled to assess their efficacy and safety in treating acute bacterial skin infections.

Oritavancin, a lipoglycopeptide, has concentration-dependent activity with bactericidal activity against gram-positive bacteria, and a prolonged half-life that allows for single-dose treatment. The SOLO I trial compared the efficacy of a single intravenous dose of 1200mg of oritavancin, with a twice daily intravenous dose of vancomycin for 7-10 days. Analysis from 950 patients found only a 1.5% difference in efficacy between the treatments (oritvancin, 82.3% compared with 78.9% for vancomycin), and a similar frequency of adverse events. A single dose of oritavancin was non-inferior to a twice daily dose of vancomycin for gram-positive skin infections.

The second drug, dalbavancin, also a lipoglycopeptide agent was tested in the DISCOVER trials. It randomised patients to receive either intravenous dalbavancin on days one and eight of treatment or intravenous vancomycin (for at least three days) with the option to switch to oral linezolid treatment. The pooled analysis showed dalbavancin efficacy was non-inferior to the vancomycin-linezolid treatment (79.1% versus 79.8%, respectively). Fewer adverse events were reported in the dalbavancin group. Intravenous doses of dalbavancin on day one and eight was non-inferior to intravenous vancomycin alongside linezolid treatment.

Corey R, Kabler H, Mehra P, et al. Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections. *NEJM.* 2014; 370:2180–90.

Boucher H, Wilcox M, Talbot G, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *NEJM.* 2014; 370:2169–79.