# Online supplement

***Systematic literature review update results***

A total of 227 and 59 articles published March 2017 to May 2020 were included in the clinical effectiveness and economic/HRQoL SLR updates, respectively. Of the 227 articles identified in the clinical SLR update, studies reported across all four MGAs: the Oncotype DX® test (n=162), MammaPrint (n=24), EndoPredict (n=29) and Prosigna (n=27). Articles reported outcomes in patients with 1-3 positive lymph nodes (n=22), lymph node negative patients (n=22) and patients with micro metastases (n=5). Outcomes reported included impact of test on treatment decision (n=80), concordance between tests (n=64) and prognostic validity (n=61). Of the 59 articles identified in the economic SLR update, studies reported across all four MGAs and reported across all of the outcomes specified; ICER (n=20), HRQoL (N=15), healthcare costs (n=12), chemotherapy costs (n=9), QALY (n=7) and utilities (n=4). Economic evaluations were performed mostly from a European perspective (n=23 studies), followed by a US (n=9), Canadian (n=6), Brazilian (n=2), Australian (n=1), Japanese (n=1), Korean (n=1) and Palestinian (n=1) healthcare perspective.

***Additional tables***

**Table S1.** Chemotherapy grade 3 or 4 adverse event costs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Adverse event | % in FEC | % with FEC-D | Unit cost | Cost sourcea |
| Alopecia | 9.0 | 10.2 | £197.70 | Outpatient visitb |
| Anaemia | 0.5 | 0.6 | £1,402.63 | HRG SA04G-L |
| Diarrhoea | 2.0 | 3.7 | £1,340.27 | HRG FD10J-M |
| Edema | 1.0 | 0.8 | £197.70 | Outpatient visit |
| Febrile neutropenia | 2.0 | 7.1 | £2,617.33 | HRG SA35A-E, non-elective long stay |
| Infection | 7.0 | 14.2 | £1,285.95 | HRG DZ22K-Q |
| Lethargy | 13.0 | 22.1 | £197.70 | Outpatient visit |
| Leukopenia | 18.0 | 24.6 | £611.46 | Outpatient and inpatient costc |
| Musculoskeletal | 1.0 | 7.0 | £197.70 | Outpatient visit |
| Myalgia/arthralgia | 0.1 | 5.0 | £197.70 | Outpatient visit |
| Nail/skin disorder | 1.0 | 3.3 | £197.70 | Outpatient visit |
| Nausea/vomiting | 10.0 | 9.7 | £1,450.61 | HRG FD11K |
| Neuropathy | 0.3 | 4.8 | £1,647.64 | HRG AA26C-H |
| Neutropenia | 40.0 | 45.5 | £473.05 | Outpatient and inpatient cost |
| Pain | 0.1 | 2.8 | £197.70 | Outpatient visit |
| Stomatitis | 2.0 | 7.6 | £2,014.64 | HRG CB01F |
| Thrombocytopenia | 0.9 | 0.6 | £1,818.52 | HRG SA12G-K |
| Fatal toxicity | 0.0 | 0.3 | £23,764.82 | Hinde et al. 1 |
| Weighted average | £731.95 | £1,344.20 | £1,045.73d |  |
| a NHS Reference costs 2019-202 by defaultb Consultant-led outpatient, medical oncologyc Assumed to be managed in inpatient setting in 11.5% of cases and in outpatient for the remaining cases (based on Copley-Merriman et al. Medicine (Baltimore) 2018;97(31):e11736; outpatient cost: NHS Reference Costs 2018-19: consultant-led outpatient, medical oncology; inpatient cost: based on Lux et al. Breast 2018;37:89-98; converted to GBP based on exchange rate GBP 1 = EUR 1.10; uplifted to 2020 prices using HCHS indexd Weighted average calculated based on distribution of chemotherapy regimens in early BCD: docetaxel 100 mg/m2; FEC: fluorouracil 500 mg/m2, epirubicin 100 mg/m2, cyclophosphamide 500 mg/m2; HRG: healthcare resource group |

**Table S2.** UK life tables, 2016-18

|  |  |
| --- | --- |
| Age | Annual rate |
| 18 | 0.000218 |
| 19 | 0.000196 |
| 20 | 0.000197 |
| 21 | 0.000224 |
| 22 | 0.000219 |
| 23 | 0.000220 |
| 24 | 0.000226 |
| 25 | 0.000260 |
| 26 | 0.000252 |
| 27 | 0.000286 |
| 28 | 0.000330 |
| 29 | 0.000314 |
| 30 | 0.000374 |
| 31 | 0.000394 |
| 32 | 0.000482 |
| 33 | 0.000500 |
| 34 | 0.000545 |
| 35 | 0.000586 |
| 36 | 0.000655 |
| 37 | 0.000738 |
| 38 | 0.000720 |
| 39 | 0.000846 |
| 40 | 0.000883 |
| 41 | 0.000993 |
| 42 | 0.001052 |
| 43 | 0.001183 |
| 44 | 0.001329 |
| 45 | 0.001437 |
| 46 | 0.001541 |
| 47 | 0.001701 |
| 48 | 0.001825 |
| 49 | 0.001937 |
| 50 | 0.002138 |
| 51 | 0.002366 |
| 52 | 0.002584 |
| 53 | 0.002759 |
| 54 | 0.002956 |
| 55 | 0.003270 |
| 56 | 0.003627 |
| 57 | 0.003903 |
| 58 | 0.004334 |
| 59 | 0.004741 |
| 60 | 0.005117 |
| 61 | 0.005615 |
| 62 | 0.006323 |
| 63 | 0.006856 |
| 64 | 0.007373 |
| 65 | 0.008027 |
| 66 | 0.008899 |
| 67 | 0.009568 |
| 68 | 0.010433 |
| 69 | 0.011426 |
| 70 | 0.012681 |
| 71 | 0.013877 |
| 72 | 0.016044 |
| 73 | 0.017700 |
| 74 | 0.019486 |
| 75 | 0.022255 |
| 76 | 0.025369 |
| 77 | 0.028178 |
| 78 | 0.031865 |
| 79 | 0.035010 |
| 80 | 0.039695 |
| 81 | 0.044925 |
| 82 | 0.051057 |
| 83 | 0.059202 |
| 84 | 0.067236 |
| 85 | 0.076619 |
| 86 | 0.087955 |
| 87 | 0.100071 |
| 88 | 0.114565 |
| 89 | 0.129490 |
| 90 | 0.147050 |
| 91 | 0.165974 |
| 92 | 0.185106 |
| 93 | 0.206525 |
| 94 | 0.230003 |
| 95 | 0.260357 |
| 96 | 0.284553 |
| 97 | 0.313245 |
| 98 | 0.339652 |
| 99 | 0.375917 |
| 100 | 0.409183 |

**Table S3.** Base case parameter values, ranges and distributions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Base case  | DSA range | PSA SE and distribution | Source |
| RS distribution |  |  |  |  |
| <11 | 17% | Not varied | Dirichlet (1619,6711,1389) | TAILORx7 |
| 11-25 | 69% |
| >25 | 14% |
| Probability of chemotherapy w/o genomic risk, LN0 | 27% | 26%,28% | Beta (α=1717;β=4612) | NCRAS, DG348 |
| Probability of chemotherapy w/o genomic risk, LN0 NPI≤3.4 | 7% | 6%, 8% | Beta (α=329;β=4248) | NCRAS, DG348 |
| Probability of chemotherapy w/o genomic risk, LN0 NPI>3.4 | 40% | 38%, 42% | Beta (α=1388;β=2018) | NCRAS, DG348 |
| Probability of chemotherapy w/o genomic risk, LNmic | 27% | 26%,28% | Beta (α=1717;β=4612) | Assumed to be the same as node-negative, clinical expert opinion |
| Probability of chemotherapy conditional on RS result |  |  |  |  |
| RS <11 | 0% | Not varied | Not varied | Clalit registry9 |
| RS 11-25 | 9% | 7%,11% | Beta (α=80;β=773) |
| RS >25 | 70% | 64%,76% | Beta (α=188;β=81) |
| 9-year DRFI with ET |  |  |  |  |
| RS <11 | 96.8% | 95%,98% | Beta (α=611;β=20) | TAILORx7  |
| RS 11-25 | 94.5% | 94%,96% | Beta (α=1964;β=114) | TAILORx7 |
| RS >25 | 62.0% | 48%,81% | Beta (α=20;β=12) | B-2010 |
| HR of DR with chemotherapy |  |  |  |  |
| RS <11 | 1.19 | 0.41,3.51 | Gamma (k=2;θ=0.53) | NASBP B-2010 |
| RS 11-25 | 0.91 | 0.71,1.18 | Gamma (k=58;θ=0.02) | TAILORx7 |
| RS >25 | 0.27 | 0.12,0.62 | Gamma (k=4;θ=0.06) | NASBP B-2010 |
| Other transition probabilities |  |  |  |  |
| Probability of local recurrence prior to distant recurrence | 10.5% | 8.8%,12.3% | Beta (α=129;β=1095) | De Bock et al.11 |
| Reduction in DR rate in years 11-15 | 50% | Not varied | Not varied | Assumption in NICE DG348 |
| Reduction in DR rate in years >15 | 50% | Not varied | Not varied | Clinical expert opinion |
| 6-month probability of AML | 0.0028 | 0.002,0.003 | Beta (α=70;β=24945) | Petrelli et al.12 |
| Probability of death, recurrence-free | See Table S7 | Not varied | Not varied | UK life tables13 |
| Median overall survival after distant recurrence (months) | 46.7 | 37,56 | Lognormal (µ=46.7;σ=0.1) | Sledge et al.14 |
| Median overall survival after AML (months) | 9.6 | 7.6,11.5 | Lognormal (µ=9.6; σ=0.1) | NICE TA55215 |
| Health state utility values |  |  |  |  |
| Recurrence-free | 0.824 | 0.785,0.857 | Beta (α=353;β=75) | Lidgren et al.16 |
| Distant recurrence | 0.685 | 0.620,0.735 | Beta (α=171;β=79) |
| AML | 0.550 | 0.504,0.596 | Beta (α=257;β=210) | NICE TA55215 |
| Utility decrements |  |  |  |  |
| Local recurrence | 0.108 | 0.028,0.188 | Beta (α=6;β=53) | Campbell et al.17 |
| Chemotherapy | 0.038 | 0.030,0.046 | Beta (α=92;β=2338) | Lidgren et al.16 |
| Unit costs |  |  |  |  |
| Test cost Oncotype DX | £2,580 | Not varied | Not varied | NICE DG348 |
| Early breast cancer chemotherapy | See Table S2 | Not varied | Not varied | N/A |
| Early breast cancer endocrine therapy | See Table S2 | Not varied | Not varied | N/A |
| Drug admin pharmacy cost | £45 | £36,£54 | Gamma (k=96;θ=0.5) | Ward et al.18 |
| First admin IV | £478 | £383,£574 | Gamma (k=96;θ=5.0) | NHS Reference costs 2019/20: SB13Z |
| Subsequent admin IV | £341 | £273,£410 | Gamma (k=96;θ=3.6) | NHS Reference costs 2019/20: SB15Z |
| Intramuscular admin | £239 | £191,£287 | Gamma (k=96;θ=2.5) | NICE TA563 6 |
| Oral admin | £0.00 | Not varied | Not varied | Assumption |
| Recurrence-free years 6+ | £0 | Not varied | Not varied | N/A |
| Local recurrence | £23,099 | £12,372,£33,826 | Gamma (k=18;θ=1297) | Karnon et al. 19 |
| Distant recurrence disease management | £3,900 | £3,120,£4,680 | Gamma (k=96;θ=41) | NICE TA563 6 |
| Distant recurrence metastatic BC chemo-endocrine therapy | £8,828 | Not varied | Not varied | See Table S5 |
| AML cost in first model cycle | £42,852 | £34,282,£51,422 | Gamma (k=96;θ=446) | Zeidan et al.20 |
| AML cost in subsequent cycles | £4,210 | £3,368,£5,052 | Gamma (k=96,θ=44) | Zeidan et al.20 |
| Terminal care | £4,916 | £3,933,£5,899 | Gamma (k=96;θ=51) | Hinde et al. 1 |
| Outpatient visit | £200 | £160,£240 | Gamma (k=96;θ=2.1) | NHS Reference costs 2019/20: service code 370 |
| LFT | £1.10 | Varied in “Total drug admin tests” | NHS Reference costs 2019/20: DAPS04 |
| U&E | £1.10 | Varied in “Total drug admin tests” |
| FBC | £2.79 | Varied in “Total drug admin tests” | NHS Reference costs 2019/20: DAPS05 |
| ECG (in 25% of patients) | £49 | Varied in “Total drug admin tests” | NHS Reference costs 2019/20: EY51Z |
| Total drug admin tests | £32 | £25,£38 | Gamma (k=96;θ=0.3) | Sum of test unit costs |
| Mammogram | £56 | £45,£67 | Gamma (k=96,θ=1) | Campbell et al.17 |
| AML: acute myeloid leukemia; DR: distant recurrence; DRFI: distant recurrence-free interval; DSA: deterministic sensitivity analysis; ECG: electrocardiogram; FBC: full blood count; HR: hazard ratio; LFT: liver function test; LN0: node-negative; LNmic: micrometastatic; NPI: Nottingham Prognostic Index; PSA: probabilistic sensitivity analysis; RS: Recurrence Score; SE: standard error; U&E: urea and electrolytes |

**Table S4.** Early breast cancer chemo-endocrine therapy cost

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value/unit cost | Cost per model cycle | Source |
| Body surface area | 1.75 |  | Assumption |
| Vial sharing | 0% |  | Assumption |
| Early BC chemotherapy regimens |  |  |  |
| FEC75 | LN0: 3% | Acquisition: £1,052; admin: £3,848 | Distributions: clinical expert opinion; calculations: see Table S3 |
| FEC-T | LN0: 21% | Acquisition: £1,734; admin: £3,848 |
| TC | LN0: 24% | Acquisition: £1,635; admin: £2,611 |
| EC90/T75 | LN0: 23% | Acquisition: £2,308; admin: £5,085 |
| EC90 | LN0: 18% | Acquisition: £760; admin: £3,023 |
| Accelerated EC/P | LN0: 8% | Acquisition: £3,537; admin: £5,085 |
| Weekly P | LN0: 3% | Acquisition: £122; admin: £7,559 |
| EC/weekly P | LN0: 3% | Acquisition: £882; admin: £10,582 |
| Early BC endocrine therapy regimens |  |  |  |
| Tamoxifen 20mg/day | 40% | Acquisition+admin: £50.96 | Distributions: NICE DG34 |
| Anastrozole 1mg/day | 20% | Acquisition+admin: £6.37 |
| Letrozole 2.5mg/day | 20% | Acquisition+admin: £10.60 |
| Exemestane 25mg/day | 20% | Acquisition+admin: £28.88 |
| Chemotherapy AE cost | See Table S1 |  |  |
| Drug unit costs | See Table S4 |  |  |
| AE: adverse event; FEC75: fluorouracil 600mg/m2, epirubicin 75mg/m2, cyclophosphamide 600mg/m; FEC-T: fluorouracil 500mg/m2, epirubicin 100mg/m2, cyclophosphamide 500mg/m2, docetaxel 100mg/m2; TC: cyclophosphamide 600mg/m2, docetaxel 75mg/m2; EC90/T75 = epirubicin 90mg/m2, cyclophosphamide 600mg/m2, docetaxel 75mg/m2; EC: epirubicin 90 mg/m², cyclophosphamide 600mg/m²; Accelerated P: paclitaxel 175mg/m²; Weekly P: paclitaxel 80mg/m² |

**Table S5.** Details of chemotherapy regimens in early breast cancer

|  |  |  |  |
| --- | --- | --- | --- |
| **Regimen** | **Dose per admin (mg)** | **No. of doses** | **Acquisition cost\*** |
| **FEC75** |  |  |  |
| Fluorouracil 600mg/m2 | 1050 | 6 | £51.48 |
| Epirubicin 75mg/m2 | 131.25 | 6 | £418.14 |
| Cyclophosphamide 600mg/m2 | 1050 | 6 | £130.68 |
| Aprepitant1 | 285 | 6 | £53.70 |
| Filgrastim1 | See below2 | 6 | £2,206.30 |
| **FEC-T** |  |  |  |
| Fluorouracil 500mg/m2 | 875 | 3 | £17.16 |
| Epirubicin 100mg/m2 | 175 | 3 | £278.76 |
| Cyclophosphamide 500mg/m2 | 875 | 3 | £40.65 |
| Docetaxel 100mg/m2 | 175 | 3 | £62.82 |
| Aprepitant | 285 | 6 | £53.70 |
| Filgrastim | See below2 | 6 | £2,206.30 |
| **TC** |  |  |  |
| Cyclophosphamide 600mg/m2 | 1050 | 4 | £87.12 |
| Docetaxel 75mg/m2 | 131.25 | 4 | £69.52 |
| Aprepitant | 285 | 4 | £35.80 |
| Filgrastim | See below2 | 4 | £1,470.87 |
| **EC90/T75** |  |  |  |
| Epirubicin 90mg/m2 | 157.50 | 4 | £371.68 |
| Cyclophosphamide 600mg/m2 | 1050 | 4 | £87.12 |
| Docetaxel 75mg/m2 | 131.25 | 4 | £69.52 |
| Aprepitant | 285 | 8 | £71.60 |
| Filgrastim | See below2 | 8 | £2,941.73 |
| **Accelerated EC90/P** |  |  |  |
| Epirubicin 90mg/m2 | 157.50 | 4 | £371.68 |
| Cyclophosphamide 600mg/m2 | 1050 | 4 | £87.12 |
| Paclitaxel 175mg/m2 | 306.25 | 4 | £121.80 |
| Aprepitant | 285 | 8 | £71.60 |
| Filgrastim | See below2 | 8 | £2,941.73 |
| **Accelerated P** |  |  |  |
| Paclitaxel 175mg/m2 | 306.25 | 6 | £182.70 |
| Aprepitant | 285 | 6 | £53.70 |
| Filgrastim | See below2 | 6 | £2,206.30 |
| **Weekly P** |  |  |  |
| Paclitaxel 80mg/m2 | 140 | 12 | £121.80 |
| FEC75: fluorouracil 600mg/m2, epirubicin 75mg/m2, cyclophosphamide 600mg/m; FEC-T: fluorouracil 500mg/m2, epirubicin 100mg/m2, cyclophosphamide 500mg/m2, docetaxel 100mg/m2; TC: cyclophosphamide 600mg/m2, docetaxel 75mg/m2; EC90/T75: epirubicin 90mg/m2, cyclophosphamide 600mg/m2, docetaxel 75mg/m2; EC: epirubicin 90 mg/m², cyclophosphamide 600mg/m²; Accelerated P: paclitaxel 175mg/m²; Weekly P: paclitaxel 80mg/m²\* Assuming no vial sharing1 Aprepitant used in 20% of anthracycline or taxane cycles; filgrastim 5 units per cycle used in 20% of anthracycline cycles, all taxane cycles and all accelerated EC/P cycles2 Dosage based on weight distribution reported by Dr. Peter Hall, Edinburgh Cancer Centre (personal communication): 19% require 5x30 MIU (1.5mg) dose, 81% require 5x48 (2.4mg) MIU dose |

**Table S6.** Drug unit costs

|  |  |  |
| --- | --- | --- |
| Drug costs | Cost per vial/pack | Source |
| Fluorouracil 500mg/10ml | £2.86 | eMIT1 |
| Epirubicin 50mg/25ml | £23.23 |
| Cyclophosphamide 1g | £13.55 |
| Cyclophosphamide 500mg | £8.23 |
| Docetaxel 160mg/8ml | £17.38 |
| Docetaxel 20mg/1ml | £3.56 |
| Paclitaxel 150mg/25ml | £10.15 |
| Capecitabine 300mg | £7.77 |
| Capecitabine 500mg | £26.30 |
| Pegylated liposomal doxorubicin 50mg/25ml infusion vials | £360.23 | BNF2 |
| Eribulin 0.88mg/2ml solution for injection vials | £361.00 |
| Tamoxifen 20mg | £4.20 | eMIT |
| Anastrozole 1mg | £0.98 |
| Letrozole 2.5mg | £1.63 |
| Exemestane 25mg | £4.76 |
| Fulvestrant 250mg/5ml solution for injection | £522.41 | BNF |
| Everolimus with examestane 5mg tablets | £2,200.00 |
| Everolimus with examestane 10mg tablets | £2,673.00 |
| Abemaciclib 150mg capsule | £1,475.00 |
| Palbociclib 125mg capsule | £2,950.00 |
| Ribociclib 200mg tablet | £983.33 |
| Aprepitant pre-made pack | £8.95 | eMIT |
| Filgrastim 300mcg/0.5ml solution for injection pre-filled syringes | £246.50 | BNF |
| Filgrastim 480mcg/0.5ml solution for injection pre-filled syringes | £395.25 |
| 1 Drugs and pharmaceutical electronic market information tool (eMIT) 32 British National Formulary 4 |

**Table S7.** Cost of treatment regimens in metastatic breast cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Drug/dosage | 1st line1 | 2nd line1 | 3rd line1 | Acquisition cost per model cycle3 | Admin cost per model cycle | Total per cycle cost |
| Chemotherapy |  |  |  |  |  |  |
| Paclitaxel 175mg/m2 monthly | 40% | 26% | 0% | £2,399.74 | £4,533.90 | £5,993.64 |
| Docetaxel 75mg/m2 monthly | 27% | 17% | 0% | £2,321.32 | £4,533.90 | £5,855.22 |
| Capecitabine 1250 mg/m2 daily | 18% | 47% | 82% | £169.04 | £0.00 | £169.04 |
| Epirubicin 90mg/m2 per + cyclophosphamide 600mg/m2 monthly  | 15% | 0% | 0% | £1,140.20 | £4,533.90 | £5,674.10 |
| Caelyx 50mg/m2 monthly | 0% | 10% | 0% | £4,322.76 | £4,533.90 | £8,856.66 |
| Eribulin 1.23mg/m2 twice/month | 0% | 0% | 18% | £12,996.00 | £8,244.84 | £21,240.84 |
| CDK4/6 inhibitors |  |  |  |  |  |  |
| Abemaciclib 150mg x 56 per month | 33.3%2 | 0% | 0% | £17,715.66 | £0.00 | £17,715.66 |
| Palbociclib 125mg x 21 per month | 33.3%2 | 0% | 0% | £17,709.78 | £0.00 | £17,709.78 |
| Ribociclib 125mg x 21 per month | 33.3%2 | 0% | 0% | £17,709.72 | £0.00 | £17,709.72 |
| Endocrine therapy |  |  |  |  |  |  |
| Tamoxifen 20mg/day | 18% | 15% | 29% | £50.96 | £0.00 | £50.96 |
| Anastrazole 1mg/day | 31% | 9% | 14% | £6.37 | £0.00 | £6.37 |
| Letrozole 2.5mg/day | 39% | 18% | 14% | £10.60 | £0.00 | £10.60 |
| Exemestane 25mg daily | 7% | 18% | 14% | £28.88 | £0.00 | £28.88 |
| Everolimus 10mg & exemestane 25mg daily | 0% | 16% | 29% | £16,245.08 | £0.00 | £16,245.08 |
| Fulvestrant 500mg x 2 doses in first month & 1 dose in months 2-6 | 4% | 23% | 0% | £3,656.87 | £238.83 | £3,895.70 |
| 1 Treatment distributions from Kurosky et al. 5 and NICE TA563 62 Assumption 3 Inclusive of G-CSF and aprepitant |

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