Potential cancer symptoms included in the study and sources of Read code lists used to define them.

We identified fatigue and 35 additional symptoms, based on symptoms listed in NICE NG 12 (2015) recommendations for suspected cancer[1–3] and additional sources,[4–6] for which Read code lists were available [7] [7,8,17,9–16].

Codes were amalgamated across sources, with minor additions by YL, CR, MB, MR, and BW. They were then deduplicated to ensure symptom definitions were mutually exclusive, and validated by clinical co-authors (YL, CR).

*Exeter University: Symptoms were defined using libraries of Read codes developed by WH and SP, and subsequently published in Moore et al 2021.*

*UCL: Additional codes were added following further empirical use by colleagues GL, CR, BW, MB, and MR.*

|  |  |
| --- | --- |
| **Symptom** | **Source of Read code list** |
| **Alarm symptoms** | |
| Abdominal (incl rectal) mass or intestinal obstruction | Renzi et al 2016 |
| Breast lump | Watson et al 2017, Exeter Uni., UCL |
| Breast skin changes | Din et al 2015 |
| Change in bowel habit | Watson et al 2017, Exeter Uni., UCL |
| Dysphagia | Watson et al 2017, Exeter Uni., UCL |
| Haematuria | Watson et al 2017, Exeter Uni., UCL |
| Haemoptysis | Watson et al 2017, Exeter Uni., UCL |
| Head or neck lump | Din et al 2015 |
| Hoarseness | Din et al 2015 |
| Jaundice | Watson et al 2017, Exeter Uni., UCL |
| Lump (excl. head & neck, breast, testicular, abdominal) | Din et al 2015 |
| Lymphadenopathy | Din et al 2015 |
| Nipple changes of concern (incl discharge or retraction) | Din et al 2015 |
| Post-menopausal bleeding | Watson et al 2017, Exeter Uni., UCL |
| Rectal bleeding | Watson et al 2017, Exeter Uni., UCL |
| Testicular enlargement/ lump | Din et al 2015 |
| **Non-alarm symptoms** | |
| Abdominal bloating | Watson et al 2017, Exeter Uni., UCL |
| Abdominal pain | Watson et al 2017, Exeter Uni., UCL Din et al 2015 Doran et al 2011 |
| Back pain | Doran et al 2011 Adapted by BW from Masefield et al 2021 |
| Chest pain | Din et al 2015 |
| Constipation | Renzi et al 2016 |
| Cough | Din et al 2015 |
| Diarrhoea | Renzi et al 2016 |
| Dyspnoea | Watson et al 2017, Exeter Uni., UCL |
| Fatigue | Exeter Uni., UCL |
| Headache | Adapted by BW from Masefield et al 2021 |
| Lower respiratory tract infection | Palin et al 2019 |
| Other musculoskeletal pain (excl back, pelvic, chest, abdominal, | Din et al 2015 Doran et al 2011 Adapted by BW from Masefield et al 2021 |
| Night sweats | Watson et al 2017, Exeter Uni., UCL |
| Pelvic pain | Din et al 2015 Zhou et al 2021 |
| Other upper gastro-intestinal (GI) symptoms (incl dyspepsia, nausea, haematemesis, vomiting, appetite loss) | Watson et al 2017, Exeter Uni., UCL Zhou et al 2021 Bouras et al 2017 Din et al 2015 |
| Testicular pain | Din et al 2015 |
| Thromboembolic disease (incl pulmonary embolism) | Hawker et al 2014, available at [Caliber PH674](https://phenotypes.healthdatagateway.org/phenotypes/PH674/version/1348/detail/) Kuan et al 2019, available at Caliber [PH338 v67](https://phenotypes.healthdatagateway.org/phenotypes/PH338/version/676/detail/) Kuan et al 2019, available at Caliber [PH71 v142](https://phenotypes.healthdatagateway.org/phenotypes/PH71/version/142/detail/) |
| Upper respiratory tract infection | Palin et al 2019 |
| Urinary Tract Infections (incl cystitis, dysuria, urgency, painful urination, urine smell) | Zhou et al 2021 |
| Weight loss | Watson et al 2017, Exeter Uni., UCL |

Bibliography

[1] National Institute for Health and Care Excellence, Suspected cancer: recognition and referral NICE Guideline Suspected cancer Contents, 2015. https://www.nice.org.uk/guidance/ng12/evidence/full-guideline-pdf-2676000277 (accessed July 7, 2020).

[2] National Institute for Health and Care Excellence, The recognition and initial management of ovarian cancer: evidence review 1 Ovarian cancer: the recognition and initial management of ovarian cancer Evidence review The recognition and initial management of ovarian cancer: evidence review 2, 2011. https://www.nice.org.uk/guidance/cg122/evidence/evidence-review-pdf-181688798 (accessed July 8, 2020).

[3] National Institute for Health and Care Excellence, Recommendations organised by symptom and findings of primary care investigations, suspected cancer: recognition and referral, (2015). https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-symptom-and-findings-of-primary-care-investigations (accessed August 5, 2020).

[4] D. Chapman, V. Poirier, D. Vulkan, K. Fitzgerald, G. Rubin, W. Hamilton, S.W. Duffy, A.H. Thomas, D. Gulliford, H. Rolfe, M. Hohmann, C. Repperday, S. Sykes, S. Taylor, A. Craig, J. Dawson, S. Forbes, H. Ryan, R. Turner, M. Ahmad, D. Chung, D. Graham, A. Millar, S. Taiyari, C.F. Smith, F. Gleeson, S. Hayles, Z. Kaveney, B. Nicholson, First results from five multidisciplinary diagnostic centre (MDC) projects for non-specific but concerning symptoms, possibly indicative of cancer, Br. J. Cancer. 123 (2020) 722–729. https://doi.org/10.1038/s41416-020-0947-y.

[5] D. Chapman, V. Poirier, K. Fitzgerald, B.D. Nicholson, W. Hamilton, Non-specific symptoms-based pathways for diagnosing less common cancers in primary care: a service evaluation, Br. J. Gen. Pract. 71 (2021) e846–e853. https://doi.org/10.3399/BJGP.2020.1108.

[6] NHS England, NHS Improvement, Rapid Diagnostic Centres: Vision and 2019/20 Implementation Specification, 2019. https://www.england.nhs.uk/wp-content/uploads/2019/07/rdc-vision-and-1920-implementation-specification.pdf (accessed September 25, 2020).

[7] S.F. Moore, S.J. Price, S. Chowienczyk, J. Bostock, W. Hamilton, The impact of changing risk thresholds on the number of people in England eligible for urgent investigation for possible cancer: an observational cross-sectional study, Br. J. Cancer. 125 (2021) 1593–1597. https://doi.org/10.1038/s41416-021-01541-4.

[8] G. Bouras, S.R. Markar, E.M. Burns, J.R. Huddy, A. Bottle, T. Athanasiou, A. Darzi, G.B. Hanna, The psychological impact of symptoms related to esophagogastric cancer resection presenting in primary care: A national linked database study, Eur. J. Surg. Oncol. 43 (2017) 454–460. https://doi.org/10.1016/J.EJSO.2016.10.010.

[9] N.U. Din, O.C. Ukoumunne, G. Rubin, W. Hamilton, B. Carter, S. Stapley, R.D. Neal, Age and Gender Variations in Cancer Diagnostic Intervals in 15 Cancers: Analysis of Data from the UK Clinical Practice Research Datalink, PLoS One. 10 (2015) e0127717. https://doi.org/10.1371/journal.pone.0127717.

[10] T. Doran, E. Kontopantelis, J.M. Valderas, S. Campbell, M. Roland, C. Salisbury, D. Reeves, Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework, BMJ. 342 (2011). https://doi.org/10.1136/BMJ.D3590.

[11] J.I. Hawker, S. Smith, G.E. Smith, R. Morbey, A.P. Johnson, D.M. Fleming, L. Shallcross, A.C. Hayward, Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations, J. Antimicrob. Chemother. 69 (2014) 3423–3430. https://doi.org/10.1093/JAC/DKU291.

[12] V. Kuan, S. Denaxas, A. Gonzalez-Izquierdo, K. Direk, O. Bhatti, S. Husain, S. Sutaria, M. Hingorani, D. Nitsch, C.A. Parisinos, R.T. Lumbers, R. Mathur, R. Sofat, J.P. Casas, I.C.K. Wong, H. Hemingway, A.D. Hingorani, A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service, Lancet Digit. Heal. 1 (2019) e63–e77. https://doi.org/10.1016/S2589-7500(19)30012-3.

[13] S.C. Masefield, S.L. Prady, T.A. Sheldon, N. Small, S. Jarvis, K.E. Pickett, The Effects of Caring for Young Children with Developmental Disabilities on Mothers’ Health and Healthcare Use: Analysis of Primary Care Data in the Born in Bradford Cohort, J. Dev. Phys. Disabil. (2021) 1–21. https://doi.org/10.1007/S10882-021-09789-7/TABLES/3.

[14] V. Palin, A. Mölter, M. Belmonte, D.M. Ashcroft, A. White, W. Welfare, T. van Staa, Antibiotic prescribing for common infections in UK general practice: variability and drivers, J. Antimicrob. Chemother. 74 (2019) 2440–2450. https://doi.org/10.1093/JAC/DKZ163.

[15] C. Renzi, G. Lyratzopoulos, T. Card, T.P.C. Chu, U. Macleod, B. Rachet, Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England, Br. J. Cancer. 115 (2016) 866–875. https://doi.org/10.1038/bjc.2016.250.

[16] J. Watson, B.D. Nicholson, W. Hamilton, S. Price, Identifying clinical features in primary care electronic health record studies: methods for codelist development, BMJ Open. 7 (2017) e019637. https://doi.org/10.1136/bmjopen-2017-019637.

[17] Y. Zhou, S.C. Mendonca, G.A. Abel, W. Hamilton, F.M. Walter, S. Johnson, J. Shelton, L. Elliss-Brookes, S. McPhail, G. Lyratzopoulos, Variation in ‘fast-track’ referrals for suspected cancer by patient characteristic and cancer diagnosis: evidence from 670 000 patients with cancers of 35 different sites, Br. J. Cancer. 118 (2018) 24–31. https://doi.org/10.1038/bjc.2017.381.