GIG CYMRU NHS WALES | Perfformiad a Gwella Performance and Improvement

# NATIONAL OPTIMAL PATHWAY FOR MALIGNANCY OF UNKNOWN ORIGIN AND CARCINOMA OF UNKNOWN PRIMARY (MUO AND CUP): 1st EDITION (2025)

## Point of Suspicion to First Definitive Treatment in Adults (aged 16 and over)

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| **Date of Issue: April 2025** |
| **Date of Review: April 2027** |
| **Owner: MUO/CUP Cancer Site Group** |

# FOREWORD

The NHS Wales National Optimal Pathways (NOPs) have been developed as part of the Suspected Cancer Pathway (SCP) programme of work. They aim to establish consistent generic and site-specific pathways that describe all routes of entry, from the point of suspicion (PoS) of cancer. They describe good practice in diagnostic and treatment pathways. The diagnostic pathway, including staging, should be performed within 28 days from PoS; and definitive treatment commenced within 21 days from date of Decision to Treat (DTT). The pathways also describe where patients should receive consistent information and support, tailored to meet their needs.

The NOPs aim to provide a platform to standardise care, reduce unwarranted variation and drive improvement whilst increasing quality across each of the cancer pathways in order to:

- meet the SCP cancer waiting time of 62 days for patients presenting with a suspicion of cancer,
- improve cancer patient experience, and,
- improve cancer patient outcomes throughout Wales to that comparable with the best outcomes in Europe.

When referring to MUO and CUP, we use the NICE guidance definitions as listed below:

**MUO - either Malignancy of Unknown Origin or Malignancy of Undefined Primary Origin:** Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.

**Provisional CUP (pCUP) - Provisional Carcinoma of Unknown Primary Origin:** Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology or cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.

**Confirmed CUP (cCUP) - Confirmed Carcinoma of Unknown Primary Origin:** Metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.

*Some MUO patients may remain MUO if they are unfit/unwilling for further investigations to identify whether they are confirmed CUP or have a site-specific cancer.*

The MUO and CUP Cancer NOP is designed to help MUO and CUP service providers and their commissioners understand the basic structure of an effective and efficient MUO and CUP cancer pathway. In essence, this optimal pathway is about ensuring that each stage of the pathway happens quickly, that communications with patients are effective and that the entire team works in a coordinated but flexible way, focusing always on the patient's journey. It is recognised that the introduction of the National Optimal Pathway for MUO and CUP Cancer may present challenges for the cancer multidisciplinary teams. However, introducing a nationally agreed, clinically endorsed pathway will support service improvement. It will also provide clarity and consistency for primary care around the referral process into secondary care, including access to diagnostics, to ensure the patients move through the system in a timely manner.

# GROUP CONSULTATION

The MUO/CUP Cancer Site Group (CSG) is led by Sonali Dasgupta, Consultant Medical Oncologist and Laura Jones, Specialist Grade Medical Oncologist. The group includes representation from the full range of professions involved in delivering cancer services. They were all able to contribute and comment on the development of the optimal pathway during a range of multi-disciplinary meetings and workshops commenced in 2021. An early draft was sent to multi-disciplinary teams (MDTs), Health Boards and Velindre NHS Trust in August 2023.

Separate workshops were also held with the Clinical Nurse Specialist (CNS) and Allied Health Professional (AHP) members to embed the Prehabilitation, Rehabilitation and Person-Centred Care (PCC) into the pathway, ensuring all patient's needs are assessed and met in a timely manner.

Following the initial draft, interim changes were discussed at the 4 monthly CSG meetings and several amendments were made to the pathway to reflect practice and to take into account views of the wider CSG group.

**Dr Sonali Dasgupta** (CSG Lead Clinician)

**Dr Laura Jones** (CSG Deputy Lead Clinician)

**Professor Tom Crosby** (National Director WCN)

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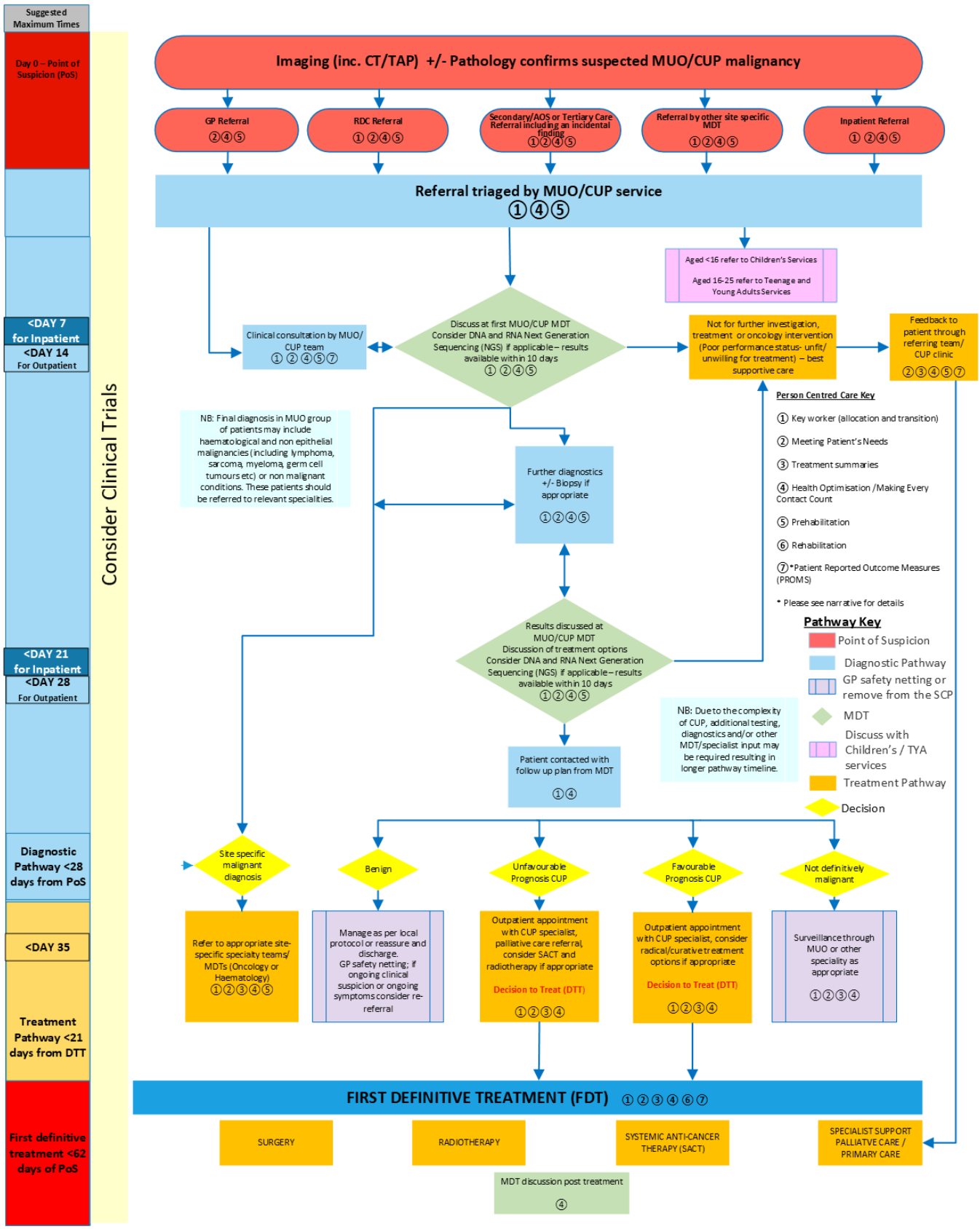
# National Optimal Cancer Pathway for Malignancy of Unknown Primary Origin (MUO) and Carcinoma of Unknown Primary (CUP): Point of Suspicion (PoS) to First Definitive Treatment (FDT) for adult patients (aged 16 and over)



# BIOMARKER TESTING

CUP patients usually have poor prognosis due to disease biology. Additionally, this is a poorly researched area with a significant unmet clinical need in optimising treatment choices and cancer outcomes. After completion of diagnostics in CUP patients, including often extensive tumour of origin (TOO) immuno-histochemistry (IHC) profiling, 20-25% patients will be diagnosed as Confirmed CUP (cCUP). Typically in this group, all investigations are complete but failed to identify a primary tumour site. For these patients, Oncologists can request CUP-specific, tumour agnostic DNA and RNA NGS panel via AWMGS.

The rationale for this approach is based on results published from the recent CUPISCO trial (Mileshkin et al, Annals of Oncol, 2023). This was a landmark multinational, prospective clinical trial recruiting cCUP patients, where after a period of induction platinum-based chemotherapy, patients were randomised between molecular guided therapy (MGT) by comprehensive genomic profiling (CGP), or standard of care chemotherapy of Oncologist's choice. Informed treatment strategies with CGP and MGT improved progression-free survival and response rates (overall survival data awaited), as compared to chemotherapy. While CUP NGS molecular profiling does not immediately allow access to targeted therapies/immunotherapies licenced for use in CUP, it allows early access for molecularly stratified clinical trials such as DETERMINE (currently recruiting in Wales).

Post diagnostic work-up, approximately one-third of the patients with diagnosis of provisional Carcinoma of Unknown Primary (pCUP) will subsequently be identified with a probable primary tumour site. Typically in this group, IHC from biopsy of one of the metastatic sites indicates a likely site-specific tumour, yet there is no visible primary tumour on scans. For these patients, site-specific DNA and RNA NGS panels can be requested according to AWMGS guidelines, to identify actionable mutations and access NICE approved therapies.

For both groups of cCUP and SST (site specific tumour)-CUPs, the recommendation for genomics should be discussed in CUP MDT and/or SST MDTs. Health Board MDTs must have an agreed method for testing and ensure results are reviewed and acted upon, with onward referral to Clinical Genetics where appropriate. Patients should be informed of the possible implications of test results for both themselves and their relatives (if applicable), ensuring relevant support and information is available.

Test request forms are available via AWMGS and should be directed to the pathology laboratory housing the tissue specimen to be tested; requests should not be directly sent to AWMGS.

# BEST PRACTICE GUIDANCE

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| **Vetting & Triage** | It is recommended that the triage of referrals is undertaken using an electronic system (e.g. Welsh Patient Referral Service) to improve the timeliness, traceability and governance of pathways.<br><br>Referrals received by MUO and CUP services should be vetted within 1-2 working days (pathway entry date: date referral originally made by primary care).<br><br>(Transition of consultant responsibility does not necessarily happen at point of discussion in MDT. However, the MDT MUO/CUP oncologist can facilitate prompt onward referral to the most appropriate team. For outpatients, at a point where a patient is seen in MUO/CUP clinic, the MUO/CUP team would assume responsibility for patient's clinical pathway/care. For patients presenting as an emergency, they would remain under the care of the admitting clinician/consultant until clearly stated by the MUO/CUP team that they have taken over care.) |
| **Additional diagnostics** | Bookings for any further diagnostics will be requested and coordinated by MUO clinic or in the absence of MUO clinic, the secondary care team and the patient will be kept fully informed. Investigations should be conducted following agreed USC principles.<br><br>Differentiating CUP from site specific metastatic malignancy can be complex and should therefore be led by experienced CUP MDT(s). |
| **Key worker role** | It is recommended that key workers facilitate additional diagnostic investigations including radiology, pathology & NGS if indicated to support MDT discussions.<br><br>Key worker will take a role in coordinating and liaising with primary and secondary care teams, other MDTs and specialist teams if their input is required.<br><br>The key worker will play a role in supporting the patient and their carers/families during the pathway process.<br><br>It is recommended that the key worker facilitates discussions with the relevant MDT members as soon as new information is available, without needing to wait until the next MDT meeting. |
| **Physiological and Symptom optimisation** | It is recommended that if diagnostic investigations (endoscopy or radiology) identify a suspected cancer, that teams give thought to patient fitness optimisation to run concurrently with pathological staging investigation. This could include consideration of the need for respiratory or cardiology (e.g. echocardiogram) investigation, nutritional support, and smoking cessation advice (if not provided previously). Additionally, consider optimisation of symptom management and palliative care referral as appropriate. |

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| **Abnormal straight to test radiology results** | Should MUO be suspected on CT-TAP imaging, a flag is advised within the radiology report, signposting the referrer to the relevant pathway, to facilitate rapid referral to appropriate team.<br><br>If an MUO cancer is suspected on straight to test radiology imaging, a process should be in place to refer the patient directly to relevant local MUO SCP services, as appropriate.<br><br>However, if a primary site is identified on subsequent radiology review, the patient should be urgently referred onwards to the relevant site-specific SCP team. |
| **Preservation of tissue for genomics** | It is recommended that the preservation of tissue for genomic testing is taken into account when preparing the initial biopsy sample. Optimal fixation time for genomics requires the specimen not be in formalin for more than 24 hours. Cutting sections up front, (to reduce waste at the microtome) and/or splitting the material over more than one block may also reduce the amount of waste at the microtome (as well as speeding up subsequent requests). Each Health Board can identify their own practice for this that is suited to local arrangements. |

# DEFINITIONS

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| **Decision to Treat** | The DATE on which a **Decision To Treat** is made. For the cancer data sets, the **DECISION TO TREAT** DATE is the DATE that the consultation between the PATIENT and the clinician took place and a Planned Cancer Treatment was agreed.<br><br>Source: NHS Data Model and Dictionary (datadictionary.nhs.uk) |
| **Direct to Test** | GPs have direct access to diagnostic endoscopy, ultrasound, MRI, X-ray and CT for people suspected of cancer.<br><br>Source: National Institute for Health and Care Excellence, Quality Standard 2016 (QS 124) |
| **First Definitive Treatment** | **First Definitive Treatment** is the **first** CLINICAL INTERVENTION intended to manage a PATIENT's disease, condition or injury and avoid further CLINICAL INTERVENTIONS. What constitutes **First Definitive Treatment** is a matter of clinical judgement in consultation with others, where appropriate, including the PATIENT.<br><br>Source: NHS Data Model and Dictionary (datadictionary.nhs.uk) |
| **Next Generation Sequencing (NGS)** | The advent of next generation sequencing (NGS) technology has revolutionised the scale at which genetic testing can be performed, enabling the analysis of many more genes within the same assay. This allows multiple variants (mutations) to be detected per sample. Large gene panel tests (>500 genes) for cancer testing are rapidly being adopted in the UK.<br><br>Source: Genome UK: the future of healthcare 2020 |

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| | AWMGS - Cymru Service for Genomic Oncology Diagnoses (CYSGODI) (medicalgenomicswales.co.uk) |
| **Safety Netting** | "Safety netting is a management strategy of patients, tests and referrals used in the context of diagnostic uncertainty in healthcare. It aims to ensure patients are monitored until signs and symptoms are explained or resolved."<br><br>Source: Royal College of General Practitioners (RCGP) - Home |
| **Straight to Test** | "Following clear referral criteria into secondary care (usually NICE guidance) the secondary care clinician (defined as per local protocol) will arrange a diagnostic procedure as the first episode of care in place of an outpatient episode. The clinician will retain clinical responsibility for the result including acting on the result."<br><br>Source: Delivering Cancer Waiting Times NHSE |
| **Teenagers and Young Adults (TYA) Service** | Young people (aged 16-24 years) with cancer have their diagnosis treatment and support agreed and delivered by a cancer-site specific multidisciplinary team and a teenage and young adult multidisciplinary team.<br><br>Source: National Institute for Health and Care Excellence (NICE), 2014. Cancer services for children and young people (QS55)<br><br>STANDARD FOR TEENAGERS AND YOUNG ADULTS WITH CANCER (nhs.wales) |
| **MUO - either Malignancy of Unknown Origin or Malignancy of Undefined Primary Origin** | Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.<br><br>*Some MUO patients may remain MUO if they are unfit/unwilling for further investigations to identify whether they are confirmed CUP or have a site-specific cancer.*<br><br>Source: Recommendations \| Metastatic malignant disease of unknown primary origin in adults: diagnosis and management \| Guidance \| NICE |
| **Provisional CUP (pCUP) - Provisional Carcinoma of Unknown Primary Origin** | Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology or cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.<br><br>Source: Recommendations \| Metastatic malignant disease of unknown primary origin in adults: diagnosis and management \| Guidance \| NICE |
| **Confirmed CUP (cCUP) - Confirmed Carcinoma of Unknown Primary Origin** | Metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.<br><br>Source: Recommendations \| Metastatic malignant disease of unknown primary origin in adults: diagnosis and management \| Guidance \| NICE |
| **Favourable CUP** | Besides single-site and oligometastatic CUP, favourable CUP is defined by obvious analogies to certain cancers with a known primary. It is generally recommended that these patients receive site-specific treatment tailored to the presumed primary site as this is associated with a more favourable prognosis compared with the vast majority of patients with CUP who are collectively grouped as 'unfavourable'. Around 20% of patients belong to one of the favourable CUP subtypes. The following favourable subtypes should be recognised |

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| | • Single metastatic deposit or oligometastatic disease amenable to local ablative treatment (single-site or oligometastatic CUP)<br>• Women with isolated axillary lymph node metastases (breast-like CUP<br>• Women with peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP)<br>• Squamous-cell carcinoma involving non-supraclavicular cervical lymph nodes (head and neck-like CUP)<br>• Men with blastic bone metastases and/or IHC or serum PSA expression (prostate-like CUP)<br>• Adenocarcinoma with colorectal IHC (CK7-negative, CK20-positive, CDX2-positive) or molecular profile (colon-like CUP)<br>• Carcinoma with renal-cell histological and immunohistochemical profile (renal-like CUP)<br><br>Source: Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up (Esmo.com) |
| **Unfavourable CUP** | Patients with unfavourable CUP are defined as those who do not belong to any of the aforementioned favourable subgroups and constitute 80% of all patients with CUP.<br><br>Source: Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up (Esmo.com) |

# CLINICAL EVIDENCE

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| **Point of Suspicion/ Referral** | The point of suspicion is when a clinician refers a patient or requests a test concerned that a patient may have cancer. Pathway start dates are defined in Appendix 1: Suspected Cancer Pathway Definitions – pathway start date (pages 23 – 29) in the following guidance:<br><br>Suspected cancer pathway: guidelines (WHC/2024/07) \| GOV.WALES<br><br>Supportive educational material is available for professionals through GatewayC.<br><br>Additional information:<br><br>Cancer Risk Assessment Tool (RAT)<br><br>Q Cancer Risk Assessment Tool |
| **Diagnosis and Management** | Metastatic malignant disease of unknown primary origin in adults: diagnosis and management. Clinical guideline CG104. Updated April 2023.<br><br>Cancer of unknown primary \| Information for the public \| Metastatic malignant disease of unknown primary origin in adults: diagnosis and management \| Guidance \| NICE<br><br>Clinical Practice Guideline – Cancers of Unknown Primary Site (esmo.org) |

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| | Metastatic malignant disease of unknown primary origin in adults: diagnosis and management (nice.org.uk) |

# PERSON CENTRED CARE

Person-centred cancer care is culturally embedded and supported by a common approach to assessing and managing people's needs and care should be co-produced to ensure people affected by cancer to achieve the outcomes that matter to them' (Cancer Quality Statement, 2021).

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| **Key Worker** | QS 14: Patients are made aware of who to contact, how to contact them and when to make contact about their ongoing healthcare needs. National Institute for Health & Care Excellence (NICE, 2012) CG138 Clinical Guideline: Patient Experience in adult NHS services<br><br>A cancer key worker is *"a person who, with the patient's consent and agreement, takes a key role in coordinating the patient's care and promoting continuity, ensuring the patient knows who to access for information and advice".*<br>1. All cancer patients must have an allocated key worker<br>2. Allocation / Review of key worker to take place at key time points including:<br>a. Around the time of diagnosis **please note: allocation of key worker **may** occur earlier than time of diagnosis, if there is a very high level of suspicion of cancer e.g. evidence obtained via pathology, radiology, endoscopy.*<br>b. Commencement of treatment<br><br>Key workers for cancer patients (Welsh Health Circular /2014/001) GOV.WALES<br><br>Cancer Improvement Plan for Wales |
| **Meeting People's Needs** | QS 4: Patients have opportunities to discuss their health beliefs, concerns and preferences to inform their individualised care.<br>QS 10: Patients have their physical and psychological needs regularly assessed and addressed, including nutrition, hydration, pain relief, personal hygiene and anxiety.<br>National Institute for Health & Care Excellence (NICE, 2012) CG138 Clinical Guideline: Patient Experience in adult NHS services<br><br>Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points including:<br>• Around diagnosis **please note: undertaking a Holistic Needs Assessment **may** occur earlier than time of diagnosis, if there is a very high level of suspicion of cancer e.g. evidence obtained via pathology, radiology, endoscopy; and it is supported by professional judgement.*<br>• At commencement, during, and at the end of treatment.<br>National Institute for Clinical Excellence (NICE, 2004) CSG4 Improving Supportive & Palliative care for adults with cancer<br><br>Ideally Holistic Needs Assessments should be undertaken electronically. Cancer Improvement Plan for Wales The Macmillan eHNA is *one* tool which is both valid and reliable. Snowden A & Fleming M (2015) Validation of the electronic HNA. |
| **Health Optimisation / MECC** | QS 9: Patients experience care that is tailored to their needs and personal preferences, taking into account their circumstances, their ability to access services and their coexisting conditions. |

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| | National Institute for Health & Care Excellence (NICE, 2012) CG138 Clinical Guideline: Patient Experience in adult NHS services<br><br>Health Optimisation refers to a proactive approach to supporting people who present to NHS services with concurrent comorbid health conditions (e.g. anaemia, diabetes), or health risk behaviours (e.g. smoking, physical inactivity).<br>Welsh Government (2018) A Healthier Wales.<br>Welsh Government (2015) Wellbeing of Future Generations Act.<br><br>Making Every Contact Count (MECC), is a behaviour change approach that helps health and social care professionals to help people to improve their health and wellbeing through prevention and early intervention. Public Health Wales Strategic Plan 2023-2026<br><br>***Lifestyle advice / resources are available*** *from* Making Every contact Count (MECC)<br><br>**Please note: Whilst addressing concurrent comorbidities and health risk behaviours is the responsibility of **all** health and social care professionals, at **every** contact throughout the pathway; earliest possible intervention **may** impact on cancer treatment choices / outcomes (especially in respect to tobacco smoking).* National Institute for Clinical Excellence (NICE, 2018) NG92 NICE Guideline Stop Smoking Interventions and services. |
| **Prehabilitation** | All patients should be given multimodal prehabilitation advice and support covering physical activity, emotional wellbeing, eating well, stopping smoking and reducing alcohol intake prior to undergoing treatment in order to enhance patient outcomes. Patient needs and goals should be evaluated on an individual basis and appropriate levels of support, from universal self-management advice to specialist support which includes timely access to allied health professional should be provided."<br>Patients should have the opportunity to take part in evidence-based education and rehabilitative activities, including self-management programmes, where available, that promote their ability to manage their own health if appropriate.<br><br>National Institute for Health & Care Excellence (NICE, 2012) CG138 Clinical Guideline: Patient Experience in adult NHS services<br><br>Welsh Government (2018) A Healthier Wales.<br>Welsh Government (2015) Wellbeing of Future Generations Act.<br>The Quality Statement for Cancer. |
| **Rehabilitation** | All patients will have their needs for rehabilitation services assessed, with referral to an appropriate level of rehabilitative support, throughout the patient pathway, including timely access to allied health professional to meet individual holistic patient needs and goals<br>**Please note: not all patients will require specialist cancer rehabilitation services. Referral into non-cancer rehabilitation, self-management, and fitness services may be suitable to meet some patients' needs.*<br>National Standards for Rehabilitation of Adult Cancer Patients (2010) GOV WALES<br>National Institute for Health and Care Excellence (NICE) CSG4 (2004) resources for improving supportive and palliative care for adults with cancer. |
| **Patient Reported Outcome Measures (PROMs) / Patient Reported** | Patient Reported Outcome Measures (PROMs) are questionnaires that patients are asked to complete **before** and **after** treatment to assess the impact on health and wellbeing.<br><br>***Some*** of the Cancer Site Groups (CSGs) have been working with the International Collaboration for Health Outcome Measurement (ICHOM), National Value in Health Team (Home - Value in Health) and other partners, to pilot tools and data capture methods, which will inform a consistent approach to PROMS for cancer. The Quallity Statement for Cancer. |

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| **Experience Measures (PREMs)** | **Please note: there are outstanding questions relating to tool selection, data capture intervals, data capture methods and data analysis / reporting which **may** prevent the implementation of PROMS & PREMS across all pathways at this time. PROMS & PREMS have been included in the pathways, in recognition of this work, and will be updated pending further advice from the CSGs.*<br><br>Patient Reported Experience Measures (PREMs) are questionnaires that patients are asked to complete at **any time** during their pathway to help professionals to understand their experience of NHS services. This information is crucial to understanding the value of healthcare as perceived by patients. Welsh Government (2024/25) People's experience framework<br><br>**Please Note: Whilst it is good practice to collect PREMS throughout the pathway, there is no current standard for cancer PREMS in Wales; further advice regarding this will be sought via the CSGs in due course.* |
| **Communication** | Clinicians must ensure patients are kept up to date about their care pathway and are supported to make individualised choices about their treatment.<br><br>Clinicians should consider the value of interventions and discuss with the patient the likely outcome of treatment options.<br><br>Clinicians in secondary and tertiary care must ensure that all decisions relating to a patient's care or treatment are communicated to the patient and their primary care clinician in a timely manner and within 24 hours of diagnosis.<br><br>Clinicians must ensure that the clinical intention of any intervention such as tests or treatment is clear to patients, and whether it is just a stage of the agreed pathway or considered start of first definitive treatment and as such ends the pathway.<br><br>Clinicians must make contemporaneous records of discussions and decisions and include reasons for deviations from recommended clinical practice in the patient's clinical record. Decisions should be made in a timely manner, and any onward referrals be completed promptly, according to local/national guidelines and optimal pathways and include adequate information to allow the receiving clinician to initiate appropriate interventions with the minimum of delay. Referrers must ensure that the patient is aware and agrees for a suspected cancer referral to be made.<br><br>Suspected cancer pathway: guidelines (WHC/2024/07) \| GOV.WALES<br><br>Metastatic malignant disease of unknown primary origin in adults: diagnosis and management. Clinical guideline CG104. Updated April 2023 |
| **Research** | Patients should have the opportunity to take part in research and clinical trials where available.<br><br>People in research \| Health Care Research Wales (healthandcareresearchwales.org)<br><br>EC Trial Finder \| ECMC (ecmcnetwork.org.uk) |