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Clinical Appropriateness Guidelines

Medical Oncology

Appropriate Use Criteria: Febrile Neutropenia Risk

Proprietary

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Table of Contents

Table of Contents	2
Description and Application of the Guidelines	3
General Clinical Guideline	4
Clinical Appropriateness Framework	4
Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions	4
Repeat Diagnostic Intervention	4
Repeat Therapeutic Intervention	5
Febrile Neutropenia Risk	6
Description and Scope	6
Clinical Indications	6
Febrile neutropenia risk	6
Febrile neutropenia risk determination for use of white blood cell growth factors for primary prophylaxis	6
Table 1. Febrile Neutropenia (FN) Risk	7
Appendix A. Guideline Notes	10
Evidence grading system: GRADE methodology	10
Breast cancer	10
High risk based on moderate-quality evidence. Estimated risk of febrile neutropenia is > 20%.Cervical cancer	11
Gastroesophageal cancer	11
Head and neck cancer	12
Non-small cell lung cancer	12
Small cell lung cancer	13
Diffuse large B-cell lymphoma	13
Ovarian cancer	13
Pancreatic cancer	14
Prostate cancer	14
Soft tissue sarcoma	14
Testicular germ cell tumors	14
References	14
Other References Reviewed	16
Codes	26
History	26

Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study

- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Febrile Neutropenia Risk

Description and Scope

These guidelines address determination of the febrile neutropenia risk that guides the use of white blood cell growth factors for oncology drug treatment regimens for adults. For interpretation of the Guidelines, and where not otherwise noted, “adult” refers to persons age 19 and older. These drug treatments may include cytotoxic chemotherapy, biologic agents, and other targeted therapies used to treat cancer. Treatments may be given orally, by injection, or by infusion. A regimen may consist of a single agent or include two or more agents.

The purpose of these guidelines is to clarify the risk categorization of cancer treatment regimens (i.e., the combination of one or more anti-cancer drugs) and to specify which patient risk factors will be taken into account when assessing regimens that are considered intermediate risk. The Guidelines are intended to be coupled with health plan policies, specific to use of white blood cell growth factors, in order to bring greater transparency to the use of risk categorization in management of this category of drugs (when used prophylactically in the setting of cancer treatment). Although there are compendia that list examples of regimens in each risk category, these judgements can be difficult due to the lack of standardization in reporting febrile neutropenia in cancer research and the lack of consensus about how to weigh different types of evidence about febrile neutropenia risk.

Clinical Indications

Febrile neutropenia risk

Febrile neutropenia risk determination for use of white blood cell growth factors for primary prophylaxis

Primary prophylaxis with white blood cell growth factors is considered medically necessary in **EITHER** of the following scenarios:

- High risk of febrile neutropenia ($\geq 20\%$) based on chemotherapy regimen
- Intermediate risk of febrile neutropenia ($\geq 10\%$ but $< 20\%$) based on chemotherapy regimen, and **ANY** of the following additional risk factors* based on literature and consensus supported guidelines, including:
 - Age > 65 years
 - Poor performance status (ECOG 3 or 4)
 - Preexisting neutropenia, for example resulting from bone marrow damage or tumor infiltration (ANC < 1500 mm³)
 - Renal dysfunction with creatinine clearance < 50 ml/min
 - Poor nutritional status (typically defined as a serum albumin ≤ 3.5 g/dL or BMI < 20)
 - Active HIV infection

*Other risk factors and risk factor definition may depend on individual guidance from other sources, such as health plan clinical criteria.

The regimen-specific risk category will be based on published information in the medical literature with the highest weight given to rigorously conducted, prospective clinical trials that include patients enrolled in the U.S. Data from retrospective studies will also be considered and evaluated according to the scientific and methodological rigor of the work.

Commonly used outpatient regimens are shown in **Table 1. Febrile Neutropenia (FN) Risk**. Regimens considered high risk or intermediate risk for febrile neutropenia are summarized in **Appendix A. Guideline**

Notes. Other selected regimens are risk-classified consistent with the NCCN as specified in the NCCN Guidelines for Hematopoietic Growth Factors.

Table 1. Febrile Neutropenia (FN) Risk

FN Risk Scenario #	Tumor Type	Regimen	Carelon FN Risk	Evidence Grade
1	Breast Cancer (metastatic)	Docetaxel (100-75 mg/m ²)	Intermediate	Moderate
2	Breast Cancer (metastatic)	Docetaxel (< 75 mg/m ²)	Low	Moderate
3	Breast Cancer (metastatic, triple-negative)	Pembrolizumab plus chemotherapy	Low	High
4	Breast Cancer (neoadjuvant or adjuvant, localized)	TCHP	High	Moderate
5	Breast Cancer (adjuvant, localized)	TC	High	Low
6	Breast Cancer (second-line, metastatic)	Trastuzumab deruxtecan	Low	High
7	Breast Cancer (second-line, metastatic, HER2-negative, locally recurrent/inoperable, metastatic)	Sacituzumab govitecan	Low	High
8	Breast cancer (neoadjuvant, localized [stage II or III], triple-negative)	Carboplatin and paclitaxel plus pembrolizumab	High	Moderate
9	Cervical Cancer (recurrent or metastatic)	Pembrolizumab and platinum-based chemotherapy +/- Bevacizumab	Low	Moderate
10	Cervical Cancer (advanced)	Cisplatin and Paclitaxel +/- Bevacizumab	Low	Moderate
11	Cervical Cancer (advanced)	Topotecan	Low	Low
12	Gastric cancer (first-line, HER2-negative, unresectable)	Nivolumab plus FOLFOX or XELOX	Low	Moderate
13	Head and Neck Squamous Cell Carcinoma (recurrent/metastatic)	Cetuximab/Panitumumab plus platinum/5FU-based chemotherapy	Low	High
14	Head and Neck Squamous Cell Carcinoma (recurrent/metastatic)	Pembrolizumab plus platinum/5FU-based chemotherapy	Low	High
15	Non-Small Cell Lung Cancer (squamous, metastatic)	Carboplatin, Paclitaxel/nab-Paclitaxel, Pembrolizumab	Low	Moderate
16	Non-Small Cell Lung Cancer (nonsquamous, metastatic)	Carboplatin, Paclitaxel, Atezolizumab +/- Bevacizumab	Low	Moderate
17	Non-Small Cell Lung Cancer (metastatic)	Carboplatin/Cisplatin, Pemetrexed, Pembrolizumab	Low	High
18	Non-Small Cell Lung Cancer	Cisplatin and Vinorelbine	Intermediate	Moderate

19	Non-Small Cell Lung Cancer (advanced)	Cisplatin and Docetaxel (60-75 mg/m ² every 21 days)	Intermediate	Moderate
20	Non-Small Cell Lung Cancer (advanced)	Docetaxel (< 100 mg/m ² every 21 days)	Intermediate	Moderate
21	Non-Small Cell Lung Cancer (advanced)	Docetaxel and Ramucirumab	Intermediate	Moderate
22	Small Cell Lung Cancer (extensive-stage)	Carboplatin, Etoposide, Atezolizumab	Low	High
23	Diffuse Large B-cell Lymphoma	GDP+/- Rituximab	Intermediate	Low
24	Ovarian Cancer (advanced)	Carboplatin and Docetaxel	Intermediate	Moderate
25	Ovarian Cancer (advanced)	Carboplatin and Paclitaxel, +/- Bevacizumab	Low	High
26	Ovarian Cancer (advanced)	Topotecan	Intermediate	Moderate
27	Pancreatic Cancer (good performance status)	FOLFIRINOX	Low	High
28	Prostate Cancer (castrate-resistant)	Cabazitaxel (20-25 mg/m ²)	Intermediate	Moderate
29	Soft Tissue Sarcoma (advanced)	Doxorubicin	Intermediate	High
30	Testicular Germ Cell Tumors (advanced)	BEP	Intermediate	Moderate
31	Testicular Germ Cell Tumors(advanced)	EP	Intermediate	Moderate

Key: BEP = bleomycin plus etoposide and cisplatin; EP = etoposide and cisplatin; FOLFOX = leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; FOLFIRINOX = leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin; GDP = gemcitabine, dexamethasone, cisplatin; TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab; TC = docetaxel and cyclophosphamide; XELOX = capecitabine (Xeloda) and oxaliplatin

Carelon FN Risk Definitions

- Febrile neutropenia (FN): Defined as single temperature: ≥ 38.3 °C orally or ≥ 38.0 °C over 1 h; and neutropenia: < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours
- Low risk for FN: Defined as a risk for FN of $< 10\%$ attributed to the treatment regimen used in a given clinical scenario
- Intermediate risk for FN: Defined as a risk of 10% - 20% attributed to the treatment regimen used in a given clinical scenario
- High risk for FN: Defined as a risk of $> 20\%$ attributed to the treatment regimen used in a given clinical scenario

Rationale

A neutrophil is a type of white blood cell that helps protect against bacterial infections. Patients receiving treatment for cancer such as chemotherapy, targeted agents, and/or radiation therapy can experience a reduction in the number of neutrophils and this may cause serious infection and even death. The lower limit of normal for the neutrophil count is 1500 per microliter of blood. Neutropenia refers to lowering of the neutrophil count, and the risk of infection is significantly increased when the neutrophil count is below 1000, and further increased when it is below 500. In addition to the degree of neutropenia, the risk of having serious infection due to low neutrophil counts varies according to factors such as the underlying type of cancer, the timing and types of cancer treatment, and the burden of other types of illness that make some patients more vulnerable to infection.¹

Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality and also a significant dose-limiting toxicity in cancer treatment. This may impact the success of treatment, particularly when treatment intent is either curative or to prolong survival. White blood cell growth factors include drugs such as pegfilgrastim (Neulasta) and filgrastim (Neupogen) and also biosimilar agents for these products. These drugs have been shown to reduce the degree and duration of neutropenia. The use of these agents and the spending on this category of supportive care products has steadily increased over the past 18 years since these drugs were introduced. These drugs are very expensive, and they are frequently overused, particularly in the U.S. The U.S. accounts for over 75% of the world's purchases of white blood cell growth factors. Health plans and some provider organizations have specific policies related to the use of white blood cell growth factors in order to reduce underutilization or overutilization of these agents.^{1, 2}

Guidelines from the American Society of Clinical Oncology (ASCO) and other organizations consider the occurrence of fever and neutropenia (so-called "febrile neutropenia") to be the clinical scenario that requires action to protect patients who may be on the verge of serious infection. The safe care of patients with febrile neutropenia requires urgent assessment and rapid administration of antibiotics. Depending on the circumstances, such patients may require evaluation in the emergency room and sometimes require hospitalization. There is general agreement among guidelines on the definition of neutropenia and the definition of fever. In the context of cancer treatment, the ASCO and other guidelines that patients at high risk for febrile neutropenia (> 20%) should receive white blood cell growth factors prophylactically (i.e., after chemotherapy but before developing symptoms or signs of febrile neutropenia). There is also agreement that those with a < 10% risk of febrile neutropenia should not receive these growth factors. Patients whose risk of febrile neutropenia is between 10%-20% are considered intermediate risk, and for those patients the use of these growth factors depends on specific patient circumstances.^{3, 4} Unfortunately, there is significant overuse of white blood cell growth factors for primary prophylaxis, particularly for patients receiving palliative chemotherapy.^{5, 6}

Several studies demonstrate that a decision support-enabled utilization management tool can improve risk-appropriate, guideline-adherent use of white blood cell growth factors.^{7, 8} ASCO recommends primary prophylaxis with a white blood cell growth factor should also be administered in patients receiving dose dense chemotherapy. ASCO also recommends consideration to alternative, equally effective, and safe chemotherapy regimens not requiring white blood cell growth factors support when available. In patients receiving concomitant chemo-radiotherapy, use of white blood cell growth factors should be avoided, especially when radiation involves the mediastinum.^{2, 4}

Appendix A. Guideline Notes

Evidence grading system: GRADE methodology

Category	Interpretation	Examples
High	Very confident that future research will not change febrile neutropenia category assignment (low, moderate, high)	Multiple consistent RCTs with methodological flaws but consistent results One or more well designed applicable RCTs
Moderate	Confident that future research is unlikely to change febrile neutropenia category assignment	RCTs with one or more reasons to downgrade evidence quality Well designed prospective studies with dramatic effect
Low	Less confident that future research will change febrile neutropenia category assignment	RCTs with two or more reasons to downgrade Well designed observational studies
Very low	Little confidence that future research will change febrile neutropenia category assignment	RCTs with three or more reasons to downgrade, poorly designed observational studies, case series

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; RCT = randomized controlled trial

Criteria – reasons to downgrade or upgrade evidence quality

- **Internal validity / Risk of bias** – methodological limitations in study design, such as incomplete randomization, high drop-out rates
- **Indirectness** – applicability of the research to the population, intervention and outcomes of interest
- **Imprecision** – confidence intervals cross a decision-making threshold, inadequate sample size
- **Inconsistency** – unexplained heterogeneity in the data
- **Publication bias** – positive selection bias in published results
- **Effect size** – dramatic effects may upgrade evidence quality

Breast cancer

Scenario 1: Metastatic breast cancer receiving single agent docetaxel (100-75 mg/m²): Intermediate

Intermediate risk based on moderate-quality evidence when the dose is 100 mg/m² every 3 weeks with estimated risk 14% (range: 6%-15%).

Scenario 2: Metastatic breast cancer receiving single agent docetaxel (< 75 mg/m²): Low

Low risk based on moderate-quality evidence when the dose is less 75 mg/m² every 3 weeks with estimated risk of 5% (range: 3%-10%).

Scenario 3: Metastatic triple-negative breast cancer treated with pembrolizumab plus chemotherapy: Low

Low risk based on high-quality evidence. Estimated risk of febrile neutropenia is 1.5%.

Scenario 4: Localized breast cancer on neoadjuvant or adjuvant TCHP: High

High risk based on moderate-quality evidence. Estimated risk of febrile neutropenia for all patients receiving TCHP was 12% (range: 6%-17%) based on moderate-quality evidence.⁸⁻¹² However, the estimated pooled risk of FN in patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence.

Scenario 5: Localized breast cancer on adjuvant TC: High

High risk based on low-quality evidence with risk estimated at 20% (range: 7%-33%). The quality of evidence is low, with limitations being related to inconsistent definitions of FN and lack of detailed reporting, and poor reporting about the rate of prophylactic use of WBC growth factors and/or prophylactic antibiotics.

Scenario 6: Metastatic breast cancer (previously treated with chemotherapy) treated with trastuzumab deruxtecan: Low

Low risk based on high-quality evidence. Estimated risk of febrile neutropenia is 1% (range: 0.3% -1.7%).

Scenario 7: Previously-treated, HER2-negative, locally recurrent, inoperable, or metastatic breast cancer treated with sacituzumab govitecan: Low

Low risk based on high-quality evidence. Estimated risk of febrile neutropenia is 4% (range: 3%-5%).

Scenario 8: Localized (stage II or III) triple-negative breast cancer treated with neoadjuvant carboplatin and paclitaxel plus pembrolizumab: High

High risk based on moderate-quality evidence. Estimated risk of febrile neutropenia is > 20%. **Cervical cancer**

Scenario 9: Recurrent or metastatic cervical cancer treated with pembrolizumab and platinum-based chemotherapy with or without bevacizumab: Low

Low risk based on moderate-quality evidence. Estimated risk of febrile neutropenia is 7.2%

Scenario 10: Advanced cervical cancer treated with cisplatin and paclitaxel with or without bevacizumab: Low

Low risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving cisplatin and paclitaxel +/- bevacizumab is 9% (range: 5%-16%) based on moderate-quality evidence. The estimation of FN is lower (< 10%) when not taking into account the Japanese trials (where neutropenia risk is generally higher based on Japanese ethnicity).

Scenario 11: Advanced cervical cancer treated with topotecan: Low

Low risk based on low-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving topotecan is 5% (range: 0%-12%) based on low-quality evidence. The estimation of febrile neutropenia is difficult based on lack of large studies, multiple dosing regimens, and atypical reporting of febrile complications.

Gastroesophageal cancer**Scenario 12: Previously untreated, unresectable, HER2-negative gastric, gastro-esophageal junction, or esophageal adenocarcinoma treated with nivolumab plus FOLFOX or XELOX: Low**

Low risk based on moderate-quality evidence. Estimated risk of febrile neutropenia is 2%.

Head and neck cancer

Scenario 13: Recurrent/metastatic head and neck cancer treated with EGFR-inhibitor (cetuximab or panitumumab) plus platinum/5FU-based chemotherapy: Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving cetuximab plus platinum-based chemotherapy is 5% (range: 2%-7%) based on high-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Scenario 14: Recurrent/metastatic head and neck cancer treated with pembrolizumab plus platinum/5FU-based chemotherapy: Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving pembrolizumab plus platinum-based chemotherapy is 9% based on high-quality evidence. Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Non-small cell lung cancer

Scenario 15: Metastatic squamous non-small cell lung cancer treated with carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab: Low

Low risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin, paclitaxel/nab-paclitaxel, and pembrolizumab is 7% (range: 3%-18%) based on moderate-quality evidence.^{13, 14}

Scenario 16: Metastatic nonsquamous non-small cell lung cancer treated with carboplatin, paclitaxel, and atezolizumab with or without bevacizumab: Low

Low risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin, paclitaxel, and atezolizumab +/- bevacizumab is 7% (range: 5%-18%) based on intermediate-quality evidence.^{15, 16} Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for imprecision.

Scenario 17: Metastatic non-small cell lung cancer treated with carboplatin/cisplatin, pemetrexed, and pembrolizumab: Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin/cisplatin, pemetrexed, and pembrolizumab is 7% (range: 0%-7%) based on high-quality evidence.^{15, 16, 17}

Scenario 18: Non-small cell lung cancer treated with cisplatin and vinorelbine: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving cisplatin and vinorelbine is 13% (range: 5%-26%) based on intermediate-quality evidence. The estimation of FN is highly dependent on dose and schedule.

Scenario 19: Advanced non-small cell lung cancer treated with cisplatin and docetaxel (with dosing in the range of 60-75 mg/m² every 21 days): Intermediate

Intermediate risk based on moderate quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving cisplatin and docetaxel for treatment advanced non-small cell lung is 10% (range: 0%-16%) based on intermediate-quality evidence. Although there is a wide range, the use of white blood cell growth factors in a subset of patients in several studies and the pooled risk known to be associated with the docetaxel alone is sufficient to put this combination regimen into the intermediate-risk category.

Scenario 20: Advanced non-small cell lung cancer treated with docetaxel at a dose of < 100 mg/m² every 21 days: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving docetaxel is 10% (range: 4%-22%) based on high-quality evidence. Whereas earlier studies produced a pooled risk closer to 7%, contemporary studies show a slightly higher risk thus shifting the risk category from low to intermediate risk.

Scenario 21: Advanced non-small cell lung cancer treated with docetaxel plus ramucirumab: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated risk of febrile neutropenia is 16%.

Small cell lung cancer

Scenario 22: Extensive-stage small cell lung cancer treated with carboplatin, etoposide, and atezolizumab: Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin, etoposide, and atezolizumab is 3% based on intermediate-quality evidence.¹⁸ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on high-quality evidence.

Diffuse large B-cell lymphoma

Scenario 23: Diffuse large B-cell lymphoma (DLBCL) treated with gemcitabine, dexamethasone, and cisplatin with or without rituximab: Intermediate

Intermediate risk based on low-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving gemcitabine, dexamethasone, and cisplatin +/- rituximab is 15% (range: 3%-36%) based on low-quality evidence. The estimation of febrile neutropenia is challenging as most trials did not clearly detail myeloid growth factor use, relatively small study population with the exception of LY.12, and large number of studies not representative of an American population.

Ovarian cancer

Scenario 24: Advanced ovarian cancer treated with carboplatin and docetaxel: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin and docetaxel is 11% (range: 0%-23%).¹⁹ Estimated pooled risk of FN in patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence, downgrade for imprecision.

Scenario 25: Advanced ovarian cancer treated with carboplatin and paclitaxel (carboplatin given at AUC 6 mg/ml/min with paclitaxel at 175 mg/m² every 3 weeks or 80 mg/m² weekly, with or without bevacizumab): Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving carboplatin and paclitaxel is 5% (range: 2%-7%) based on high-quality evidence.¹⁹⁻²⁵ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence.

Scenario 26: Advanced ovarian cancer treated with topotecan: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving topotecan is 4% (range: 1%-18%) based on intermediate-quality evidence.²⁶⁻³⁰ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for applicability (dosing regimen).

Pancreatic cancer

Scenario 27: Pancreatic cancer patients with good performance status treated with FOLFIRINOX: Low

Low risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving FOLFIRINOX was 6% (range: 2%-17%) based on moderate-quality evidence.³¹⁻³⁵ Estimated pooled risk of FN in patients not receiving primary prophylaxis is < 10% based on moderate-quality evidence, downgrade for imprecision and heterogeneity.

Prostate cancer

Scenario 28: Castrate-resistant prostate cancer (CRPC) treated with cabazitaxel (20-25 mg/m²): Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving cabazitaxel dosed at 20-25 mg/m² is 8% (range: 1.4%-18%) based on moderate-quality evidence.

Soft tissue sarcoma

Scenario 29: Advanced soft tissue sarcoma treated with doxorubicin: Intermediate

Intermediate risk based on high-quality evidence. Estimated pooled risk of febrile neutropenia for patients not receiving primary prophylaxis treated with single agent doxorubicin is 13% (9%-20%) based on high-quality evidence.

Testicular germ cell tumors

Scenario 30: Advanced testicular germ cell tumors treated with bleomycin, etoposide, and cisplatin: Intermediate

Intermediate risk based on moderate quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving bleomycin, etoposide, and cisplatin is 15% (range: 5%-20%) based on moderate-quality evidence. The estimated pooled risk of FN for patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence.

Scenario 31: Advanced testicular germ cell tumors treated with etoposide and cisplatin: Intermediate

Intermediate risk based on moderate-quality evidence. Estimated pooled risk of febrile neutropenia for all patients receiving etoposide and cisplatin is 15% (range: 3%-23%) based on moderate-quality evidence. The estimated pooled risk of FN for patients not receiving primary prophylaxis is 10%-20% based on moderate-quality evidence.

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT

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96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection [Neulasta OnPro injector]
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HCPCS

J1442	Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram [Neupogen]
J1447	Injection, tbo-filgrastim, 1 microgram [Granix]
J2505	Injection, pegfilgrastim, 6 mg [Neulasta]
J2820	Injection, sargramostim (GM-CSF), 50 mcg [Leukine, Prokine]
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (ziextenzo), 0.5 mg
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (nyvepria), 0.5 mg

ICD-10 Diagnosis

All diagnoses

History

Status	Review Date	Effective Date	Action
Revised	10/23/2023	02/01/2024	Independent Multispecialty Physician Panel (IMPP) review. Changes made to the following sections: Breast Cancer, Cervical Cancer, Gastroesophageal Cancer, and Non-small cell lung cancer.
Created	02/03/2020	07/01/2021	IMPP review. Original effective date.