Oncology Clinical Pathways
Plasma Cell Disorders

April 2025 – V1.2025

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Plasma Cell Disorders – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- Multiple myeloma

Vietnam Veterans – Agent Orange Exposure or Specified Locations

- AL Amyloidosis
- Multiple myeloma
- Monoclonal gammopathy of undetermined significance (MGUS)

Gulf War and Post 9/11 Veterans

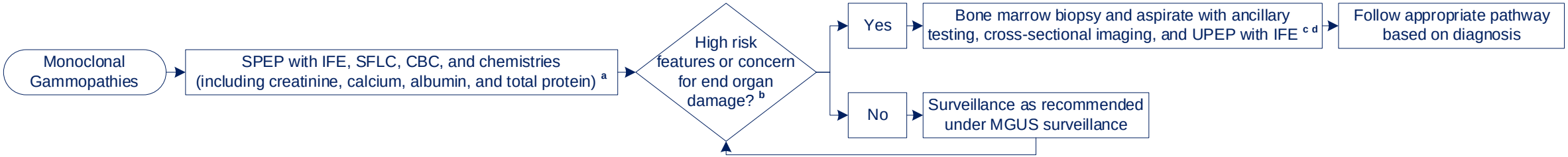
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Multiple myelomas, including monoclonal gammopathy of undetermined significance (MGUS)

*The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov); VA makes several cancers presumptive for service connection Jan 08 2025; eCFR :: 38 CFR 3.320b -- Presumptive service connection for leukemias, multiple myelomas, myelodysplastic syndromes, and myelofibrosis.

Plasma Cell Disorders – Monoclonal Gammopathies



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Consider Additional Lab Tests** including quantitative immunoglobulins, UPEP with IFE depending on the clinical scenario; **consider cross-sectional imaging** for IgM monoclonal gammopathy

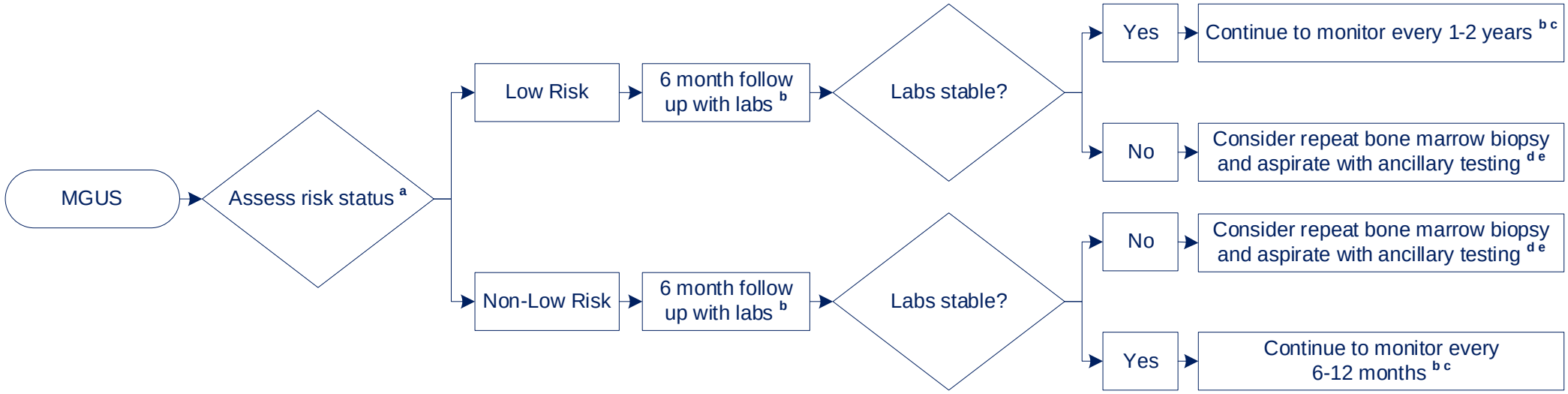
[b] **High Risk** based on risk stratification models that incorporate M-spike level and involved immunoglobulin

[c] **Ancillary Testing** includes myeloma FISH panel, karyotype, and flow cytometry; myeloma FISH panel should include at minimum: 17p (TP53), del 13, 1q21, 1p, and t(11;14); also either upfront or reflex testing for t(4;14), t(14;16), and t(14;20)

[d] **Imaging** PET/CT vertex to toes, whole body MRI, or whole body low-dose non-contrast CT

SPEP Serum Protein Electrophoresis
IFE Immunofixation Electrophoresis
SFLC Serum Free Light Chain
CBC Complete Blood Count
UPEP Urine Protein Electrophoresis
MGUS Monoclonal Gammopathy of Undetermined Significance

Plasma Cell Disorders – MGUS



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[a] **Risk Stratification** based on involved immunoglobulin and level of monoclonal protein

[b] **Follow Up with Labs** measurement of monoclonal protein (e.g. SPEP, SFLC, quantitative immunoglobulins), CBC, and chemistries (including SCr and Ca)

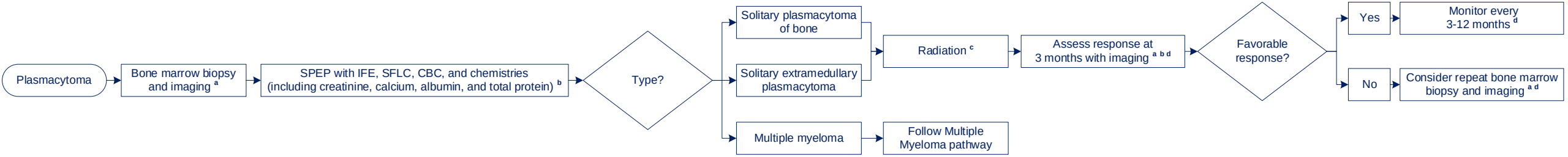
[c] **Monitoring** if expected life expectancy is <5 years, consider discontinuing monitoring

[d] **Ancillary Testing** includes myeloma FISH panel, karyotype, and flow cytometry; myeloma FISH panel should include at minimum: 17p (TP53), del 13, 1q21, 1p, and t(11;14); also either upfront or reflex testing for t(4;14), t(14;16), and t(14;20)

[e] **Imaging** PET/CT vertex to toes, whole body MRI, or whole body low-dose non-contrast CT

MGUS Monoclonal Gammopathy of Undetermined Significance
SPEP Serum Protein Electrophoresis
SFLC Serum Free Light Chain
CBC Complete Blood Count

Plasma Cell Disorders – Plasmacytoma



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[a] **Imaging** PET/CT, whole body MRI, or whole body non-contrast CT

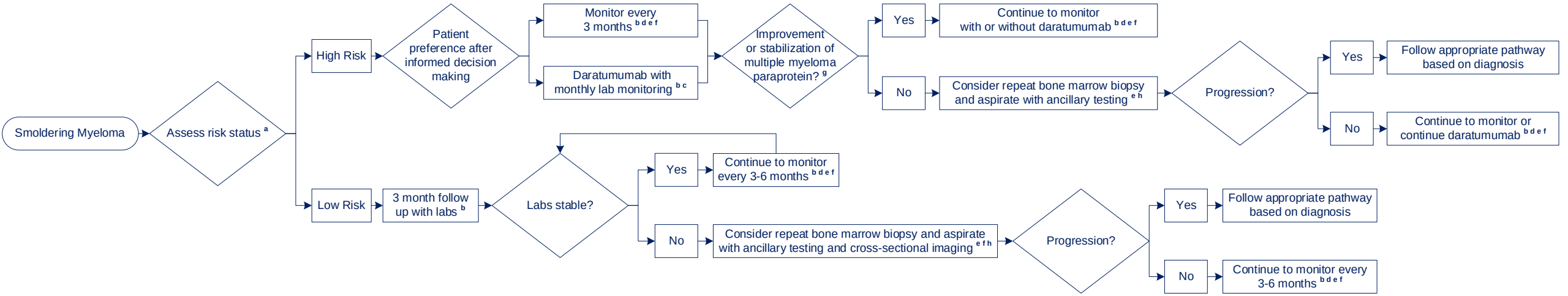
[b] **Consider Additional Lab Tests** including quantitative immunoglobulins, UPEP, and IFE depending on the clinical scenario

[c] **Radiation** if solitary plasmacytoma of bone is less ≤ 5cm dose with 35-40Gy; if > 5cm 40-50Gy; if solitary extramedullary plasmacytoma dose 40-50Gy regardless of size

[d] **Monitoring** assess response with imaging after completion of radiation; SPEP with IFE, SFLC, CBC, and chemistries (including creatinine, calcium, albumin, and total protein)

SPEP Serum Protein Electrophoresis
IFE Immunofixation Electrophoresis
SFLC Serum Free Light Chain
CBC Complete Blood Count
UPEP Urine Protein Electrophoresis

Plasma Cell Disorders – Smoldering Myeloma



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[a] **Risk Stratification** high risk defined as bone marrow plasma cells >20%, monoclonal protein >2 g/dL, and SFLC ratio >20 (involved/uninvolved light chain)

[b] **Follow Up with Labs** measurement of monoclonal protein (e.g. SPEP, SFLC, quantitative immunoglobulins), CBC, and chemistries (including SCr and Ca)

[c] **Daratumumab** (daratumumab/hyaluronidase subcutaneous) obtain Hepatitis B serology, T&S and antibody screen required prior to initiation; daratumumab can affect quantification of SPEP M-spike; shared decision making is recommended; the phase III AQUILA trial utilized daratumumab/hyaluronidase 36 months vs active monitoring and showed a PFS and OS benefit in patients who received daratumumab/hyaluronidase; patients receiving daratumumab/hyaluronidase had increased risk of infection; in addition, the definition of high risk in this trial was broader than in footnote a; however, in subgroup analysis, the benefit was most pronounced in patients who would have been high risk based on footnote a

[d] **Consider Additional Lab Tests** including quantitative immunoglobulins, UPEP, and IFE depending on the clinical scenario; **consider yearly cross-sectional imaging** (e.g. PET/CT vertex to toes, whole body MRI, or whole body low-dose non-contrast CT)

[e] **Monitoring** if expected life expectancy is <5 years, consider discontinuing monitoring

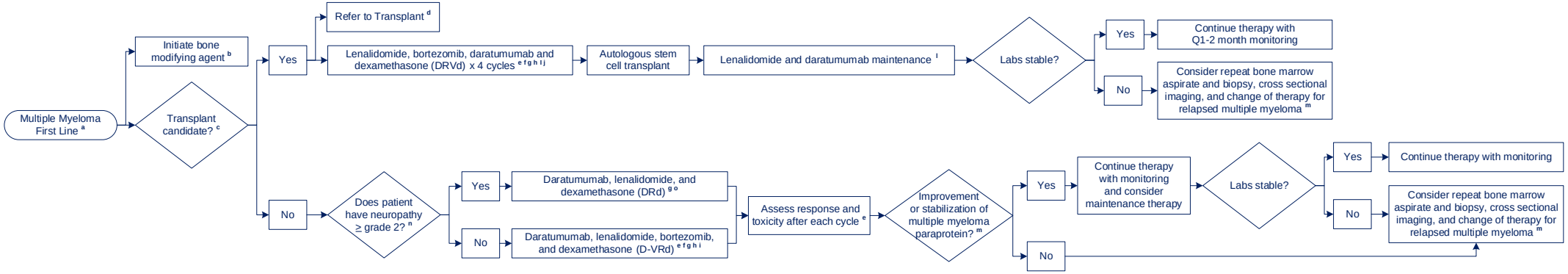
[f] **Imaging** PET/CT vertex to toes, whole body MRI, or whole body low-dose non-contrast CT

[g] **Improvement or Stabilization of Multiple Myeloma Paraprotein** based on SPEP, SFLC, UPEP, quantitative immunoglobulins

[h] **Ancillary Testing** includes myeloma FISH panel, karyotype, and flow cytometry; myeloma FISH panel should include at minimum: 17p (TP53), del 13, 1q21, 1p, and t(11;14); also either upfront or reflex testing for t(4;14), t(14;16), and t(14;20)

SPEP Serum Protein Electrophoresis
SFLC Serum Free Light Chain
CBC Complete Blood Count
IFE Immunofixation Electrophoresis
UPEP Urine Protein Electrophoresis

Plasma Cell Disorders – Multiple Myeloma, First Line



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Multiple Myeloma** bone marrow biopsy for diagnosis required; consider Congo Red if amyloidosis is clinically or histologically suspected; consider CD138 immunohistochemistry for suboptimal BM aspirate or apparent discordance between aspirate smear and core biopsy

[b] **Bone Protective Agent** dental evaluation and serum calcium with vitamin D level required before initiation; assess kidney function; preferred agent is zoledronic acid (if CrCl < 30 ml/min, use denosumab or pamidronate)

[c] **Transplant Eligibility** discuss with transplant team if needed; discourage use of tobacco, alcohol, or illicit drugs

[d] **Transplant** early referral recommended; transplant can occur early or delayed based on patient discussion with Transplant team; post-transplant consolidation and/or maintenance timing and selection should occur in consultation with Transplant team; referral for cellular therapy (stem cell transplant, CAR T-cell therapy) requires pre-transplant evaluation and review through TRACER

[e] **Assessment of Response** includes SPEP, SFLC, and/or UPEP as appropriate; assessment of toxicity includes assessing cytopenias, neuropathy, Venous Thromboembolism (VTE), infections

[f] **RVd or KRd** thromboprophylaxis and VZV prophylaxis required; consider PJP prophylaxis; consider dose reduction of lenalidomide based on renal function; consider dose reduction of dexamethasone based on age

[g] **Supportive Care and Treatment Modification Considerations**
- Thromboprophylaxis required with IMIDs (e.g., lenalidomide, pomalidomide); options include aspirin, enoxaparin, or DOAC; DOAC preferred when IMID is paired with Carfilzomib due to higher thrombosis risk
- VZV prophylaxis is required with proteosome inhibitors (e.g., bortezomib, carfilzomib) and with CD38 antibodies (e.g., daratumumab)
- PJP prophylaxis recommended due to ongoing/chronic dexamethasone use.
- Lenalidomide requires dose reduction/modification based on renal function
- Dexamethasone should be dose reduced to 20 mg weekly for age >75 years
- Once multiple myeloma response has been reached, dexamethasone dosing frequency should be reduced or even discontinued to reduce risk of infections
- Bortezomib should be administered subcutaneously to reduce risk of neuropathy; consider weekly bortezomib administration to reduce risk of neuropathy; available data show that weekly bortezomib does not reduce efficacy
- Subcutaneous daratumumab is preferred over daratumumab due to reduced adverse reactions and faster administration
- Type and Screen (T&S) and antibody screen and hepatitis B serologies prior to daratumumab or daratumumab administration
- Palliative XRT for painful osseous lesions; minimize bone marrow exposure, especially of the pelvis, in patients who are transplant candidates
- Consider IVIG for patients with hypogammaglobulinemia of the uninvolved immunoglobulins and recurrent infections

[h] **VCd or RVd** consider weekly bortezomib and subcutaneous administration of bortezomib to reduce neuropathy; available data show that weekly bortezomib does not reduce efficacy

[i] **Cyclophosphamide, bortezomib, dexamethasone** is an option if renal function prohibits lenalidomide use; if renal function improves, switching to a lenalidomide-containing regimen is encouraged

[j] **Continue Therapy** with assessment of response and toxicity after each cycle; continued communication with Transplant team

[k] **Risk Assessment** by R-ISS (Serum Beta-2 Microglobulin (B2M), LDH, myeloma FISH, and albumin); if not already complete, obtain CBC, chemistries (including SCr and Ca), cross sectional imaging (PET/CT, whole body MRI, or whole non-contrast CT), measure of monoclonal protein (SPEP, SFLC, Quantitative immunoglobulins, and/or UPEP); myeloma FISH panel should include at minimum: 17p (TP53), del 13, 1q21, 1p, and t(11;14); t(4;14), t(14;16), and t(14;20)

[l] **Lenalidomide and Daratumumab Maintenance** is 2 years followed by lenalidomide alone until progression

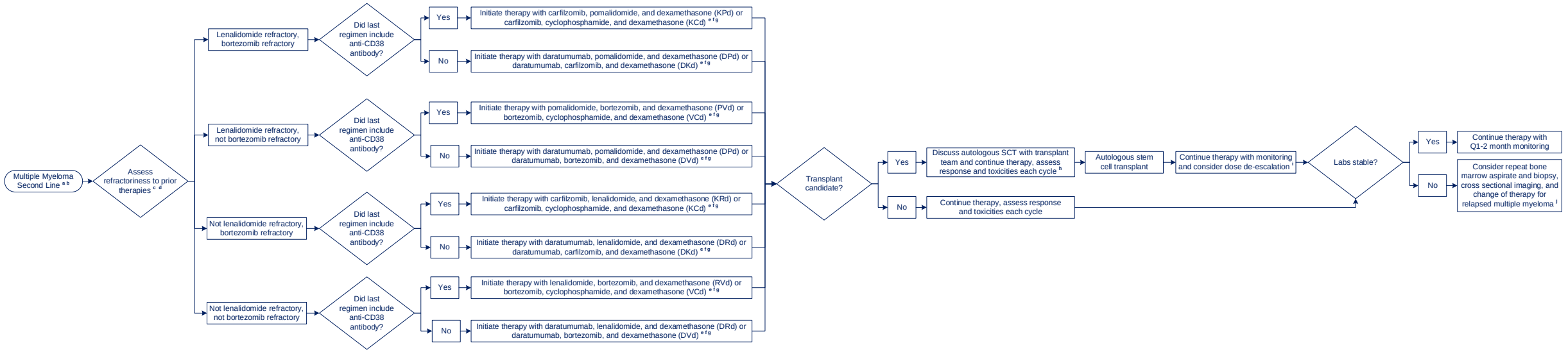
[m] **Improvement or Stabilization of Multiple Myeloma Paraprotein** based on SPEP, SFLC, UPEP, quantitative immunoglobulins

[n] **Grade 2 Neuropathy** moderate symptoms or limiting instrumental ADLs

[o] **DRd** thromboprophylaxis and VZV prophylaxis required; consider PJP prophylaxis. Hepatitis B serology, Type and Screen (T&S) and antibody screen required prior to initiation; consider dose reduction of lenalidomide based on renal function; consider dose reduction of dexamethasone based on age; daratumumab can affect quantification of SPEP M-spike

DOAC Direct Oral Anticoagulant
SPEP Serum Protein Electrophoresis
SFLC Serum Free Light Chain

Plasma Cell Disorders – Multiple Myeloma, Second Line Relapsed



Clinical trial(s) and shared decision making always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Supportive Care** should be provided to all myeloma patients receiving therapy

[b] **Subsequent Therapy** consider the following when selecting subsequent therapy:
- Triplet therapy is usually considered more effective than doublet therapy
- CD38 antibody based therapy regimens should be considered if not previously administered
- Alternate combination of drug classes or alternate drugs within a class when selecting a new treatment regimen (i.e., immunomodulatory agents, proteosome inhibitors, CD38 antibodies, alkylator chemotherapy, and others)
- Route and frequency of administration of new treatment regimens to align with patient preferences in therapy
- Dose reduction may be needed to continue therapy in the face of adverse events and prior toxicities

[c] **Consideration of Alternate Treatment** based on duration and/or depth of response to prior therapy and toxicities

[d] **Assessment of Response** includes SPEP, SFLC, and/or UPEP as appropriate; assessment of toxicity includes assessing cytopenias, neuropathy, Venous Thromboembolism (VTE), infections

[e] **Treat Until Intolerance or Progression** consider reduction or elimination of dexamethasone for patients responding well to therapy after at least six cycles

[f] **Assess** patient comorbidities, multiple myeloma predictive/prognostic factors, and patient preference

[g] **Factors that Affect Therapeutic Choice** patient comorbidities neuropathy: avoid bortezomib, cardiopulmonary disease: avoid carfilzomib Multiple Myeloma Predictive/Prognostic Factors: high risk cytogenetics: favor bortezomib or carfilzomib based regimens, presence of t(11;14): consider venetoclax based regimen; Patient Preference: consider regimens that are administered only in clinic depending on patient preference

[h] **Referral for Cellular Therapy** (stem cell transplant, CAR T-cell therapy) requires pre-transplant evaluation and review through TRACER

[i] **De-Escalation of Frequency** or dose of dexamethasone is often performed to reduce side effects of long-term dexamethasone use; de-escalation of other components of therapy typically occur for side effects, in order to maintain duration of therapy

[j] **Relapsed Multiple Myeloma** consider repeat bone marrow aspirate and biopsy, cross sectional imaging, and change of therapy for relapsed multiple myeloma

[k] **Supportive Care and Treatment Modification Considerations**
- Thromboprophylaxis required with IMIDs (e.g., lenalidomide, pomalidomide); options include aspirin, enoxaparin, or DOAC; DOAC preferred when IMID is paired with Carfilzomib due to higher thrombosis risk
- VZV prophylaxis is required with proteosome inhibitors (e.g., bortezomib, carfilzomib) and with CD38 antibodies (e.g., daratumumab)
- PJP prophylaxis recommended due to ongoing/chronic dexamethasone use.
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- Consider IVIG for patients with hypogammaglobulinemia of the uninvolved immunoglobulins and recurrent infections

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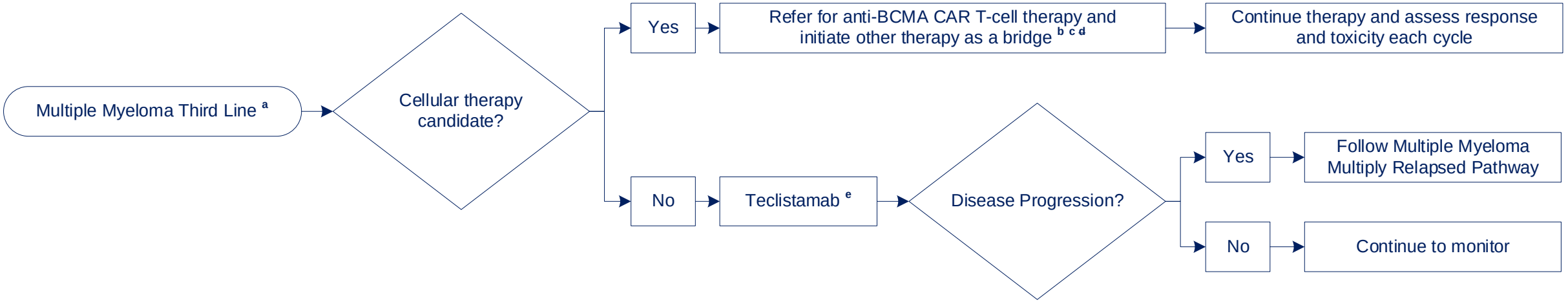
SPEP Serum Protein Electrophoresis
SFLC Serum Free Light Chain

Plasma Cell Disorders – Multiple Myeloma, Third Line



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[a] **Supportive Care** supportive care should be continued for all myeloma patients receiving therapy; referral to palliative care recommended; review molecular testing from last bone marrow biopsy

[b] **CAR T-Cell Therapy** is associated with risk of cytokine release syndrome and neurotoxicity, and requires inpatient hospitalization for monitoring

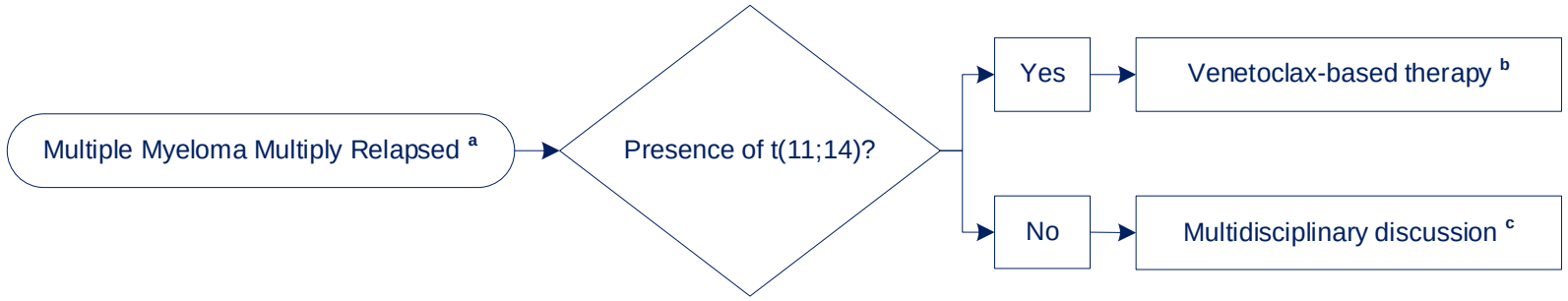
[c] **Refer for Cellular Therapy** (stem cell transplant, CAR T-cell therapy) requires pre-transplant evaluation and review through TRACER

[d] **Venetoclax** requires TLS monitoring during ramp-up period and is associated with risk of infections; anti-viral prophylaxis is highly recommended; growth factor support may be used for cytopenias

[e] **Teclistamab** requires facility support and protocols for monitoring of and management of cytokine release syndrome and CNS toxicity and resultant immunosuppression

BCMA B-Cell Maturation Antigen
CAR T-Cell Chimeric Antigen Receptor T-cell

Plasma Cell Disorders – Multiple Myeloma, Multiply Relapsed



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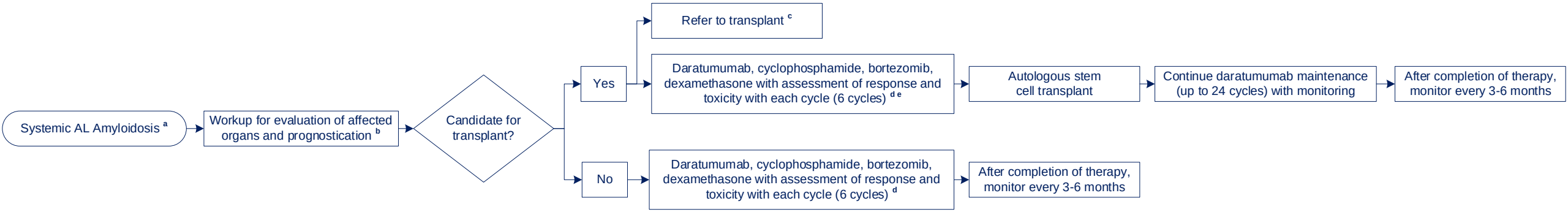
[a] **Supportive Care** supportive care should be continued for all myeloma patients receiving therapy; referral to palliative care recommended; review molecular testing from last bone marrow biopsy

[b] **Venetoclax** requires TLS monitoring during ramp-up period and is associated with risk of infections; anti-viral prophylaxis is highly recommended; growth factor support may be used for cytopenias

[c] **Multidisciplinary Discussion** consider CAR T or bispecific antibody if not previously received and candidate; consider NTO hematology tumor board presentation

Plasma Cell Disorders – Systemic AL Amyloidosis



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[a] **Systemic AL Amyloidosis** pathway does not apply to other forms of amyloidosis, including TTR and AA amyloidosis; diagnosis of AL amyloidosis requires biopsy of the affected organ with congo red staining and mass spectroscopy demonstrating light chain and amyloid deposition; fat pad biopsy can be helpful if biopsy of affected organ is dangerous, impossible, or non-diagnostic

[b] **Workup** includes evaluation of affected organs as directed by symptoms (e.g., nerve or GI involvement) and including evaluation for kidney impairment, nephrotic range proteinuria (e.g., urine protein/creatinine ratio or 24 hour urine collection), cardiac involvement (e.g., transthoracic echocardiogram and/or cardiac MRI, BNP, troponin I), and evaluation for bone marrow involvement/multiple myeloma including molecular testing (see initial multiple myeloma pathway)

[c] **Transplant** referral for stem cell transplant requires pre-transplant evaluation and review through TRACER

[d] **Supportive Care and Treatment Modification Considerations**
- VZV prophylaxis is required with proteosome inhibitors (e.g., bortezomib, carfilzomib) and with CD38 antibodies (e.g., daratumumab)
- PJP prophylaxis recommended due to ongoing/chronic dexamethasone use.
- Dexamethasone should be dose reduced to 20 mg weekly for age >75 years
- Bortezomib should be administered subcutaneously to reduce risk of neuropathy. Consider weekly bortezomib administration to reduce risk of neuropathy
- Subcutaneous daratumumab is preferred over daratumumab due to reduced adverse reactions and faster administration
- Type and Screen (T&S) and antibody screen and hepatitis B serologies prior to daratumumab or daratumumab administration

[e] **Continue Therapy** with assessment of response and toxicity after each cycle; continued communication with Transplant team

Plasma Cell Disorders – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Patients who have had a bone marrow biopsy to work up a plasma cell disorder, including: 1.) Monoclonal Gammopathies of Undetermined Significance (MGUS) 2.) Plasmacytoma 3.) Smoldering Myeloma 4.) Multiple Myeloma - First Line (and second line if not performed earlier)	FISH	FISH panel should be performed on CD138-sorted cells and include 17p (TP53), del 13, 1q21, 1p, and t(11;14). Additional upfront or reflex testing for t(4;14), t(14;16), and t(14;20)	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Flow cytometry	Flow cytometry	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood
	Karyotyping	Karyotyping	Local VA or locally contracted vendor	No	Bone Marrow Biopsy, Lymph Node Biopsy, Blood