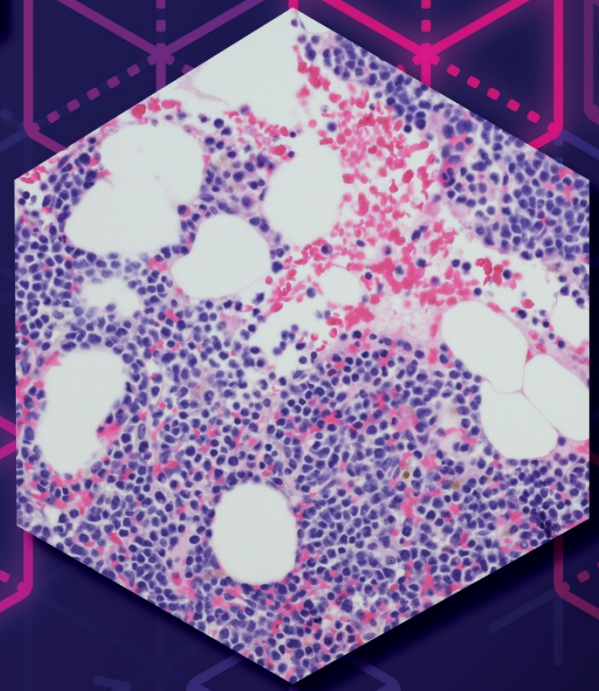
The Multiple Myeloma Treatment Paradigm:

Addressing an Evolving and Multifaceted Process



Jointly provided by

Impact Education LLC

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

This activity is supported by an independent educational grant from Celgene Corporation.

Live Webcast

Treatment Sequences and Combinations in Multiple Myeloma Management

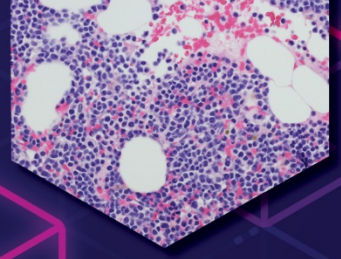
David Vesole, MD, PhD

Co-Chief, Myeloma Division, and Director, Myeloma Research, John Theurer Cancer Center at Hackensack UMC

Director, Myeloma Program, Medstar Georgetown University Hospital

Professor, Georgetown University School of Medicine

Pathophysiology: Natural History



Monoclonal gammopathy of undetermined significance (MGUS)

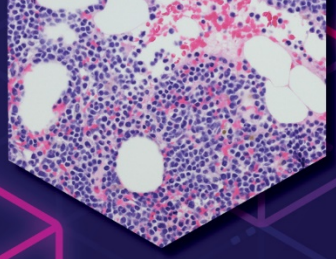
- 1-2% per year progress to MM
- 11% progress over lifetime

Smoldering Multiple Myeloma

- 10% per year progress to MM
- 73% progress within 15 years

Multiple Myeloma

Pathophysiology: Clinical Sequelae



Plasma Cell Proliferation

- Osteolytic lesions
- Hypercalcemia
- Anemia
- Plasmacytomas
- Hyperviscosity
- Cryoglobulinemia

Bone Marrow Infiltration

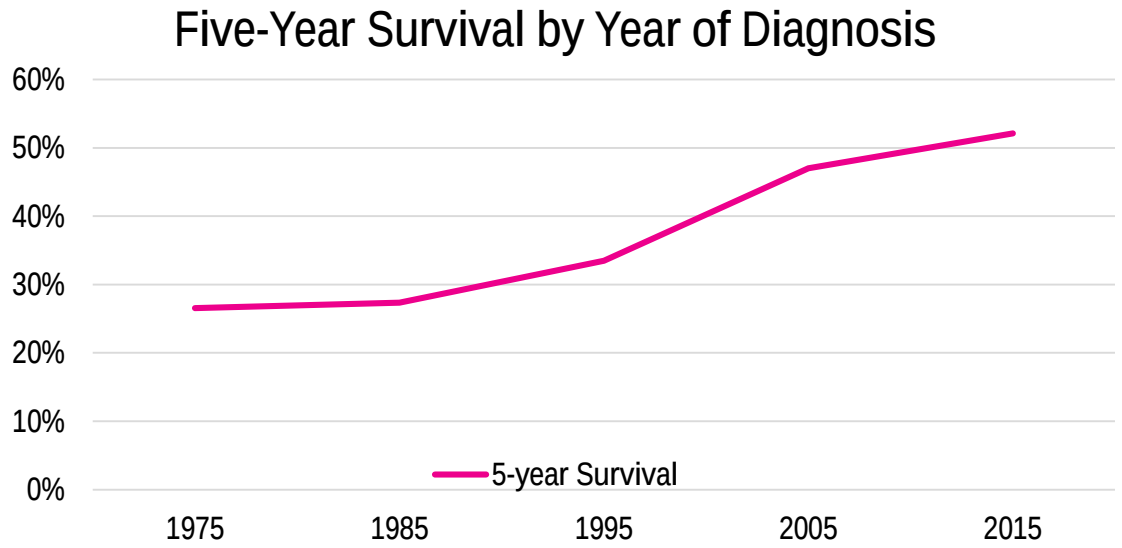
- Anemia
- Neutropenia
- Thrombocytopenia

M Protein

- Nephropathy
- Hyperuricemia
- Amyloidosis
- Glomerulosclerosis

Epidemiology

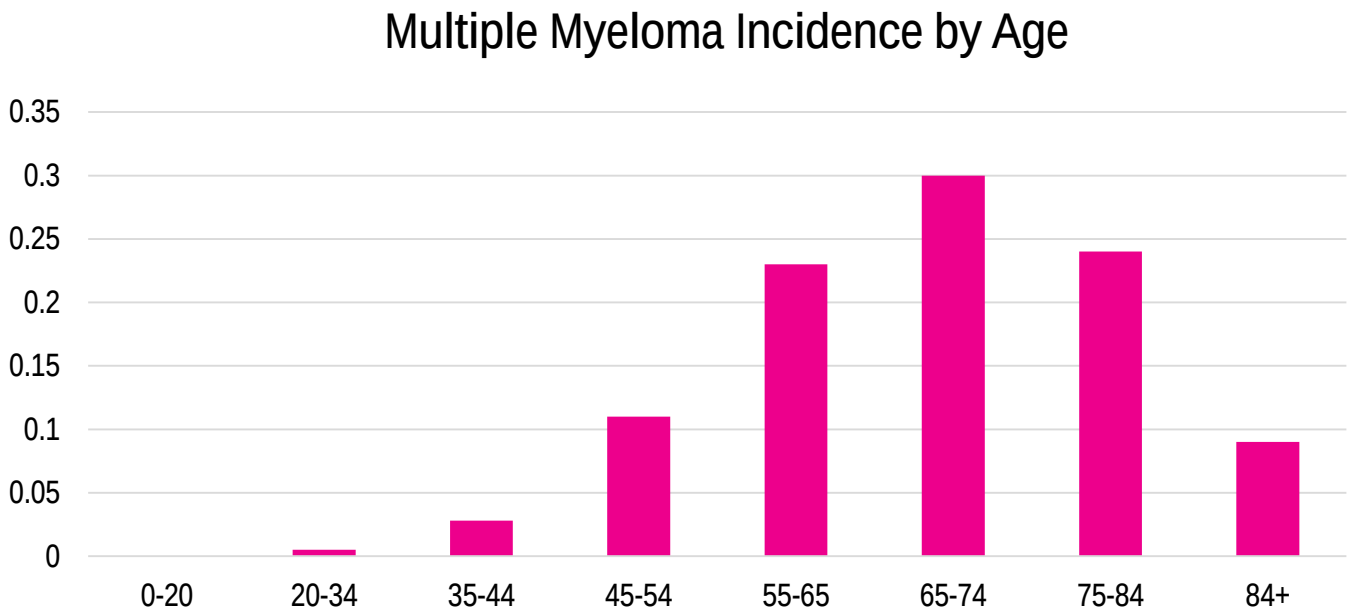
- National Cancer Institute: 30,770 new cases in 2018
- 12,770 deaths annually
- 13% of hematological cancers and 20% hematologic malignancy deaths
- 5-year overall survival 50%+



Cancer Stat Facts: Myeloma. National Cancer Institute Surveillance, Epidemiology, and End Results Program website. https://seer.cancer.gov/statfacts/html/mulmy.html. Published April 2018. Accessed September 2018.

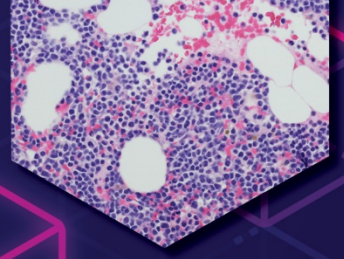
Patient Characteristics

- More common in men: 16,400 men;14,370 women in 2018
- 2x greater risk in African-Americans
- Average age 69



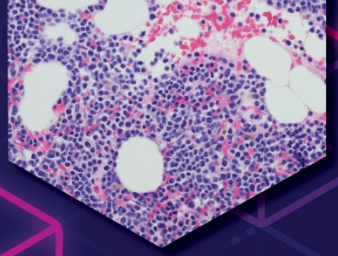
Cancer Stat Facts: Myeloma. National Cancer Institute Surveillance, Epidemiology, and End Results Program website. https://seer.cancer.gov/statfacts/html/mulmy.html. Published April 2018. Accessed September 2018.

Special Considerations for Smoldering MM



- Enroll in clinical trial or follow up every 3-6 months with at least:
  - CBC with differential and platelet count
  - Serum creatinine and serum calcium levels
  - Serum quantitative immunoglobulins, SPEP, SIFE
  - 24-hour urine for total protein, UPEP, UIFE
- As indicated, also include:
  - Serum FLC assay
  - Skeletal survey or whole-body low-dose CT scan and/or whole-body or skeletal MRI or PET/CT scan
  - Bone marrow aspirate and biopsy with FISH and multi-parameter flow cytometry

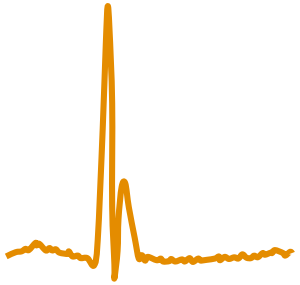
A Diagnosis



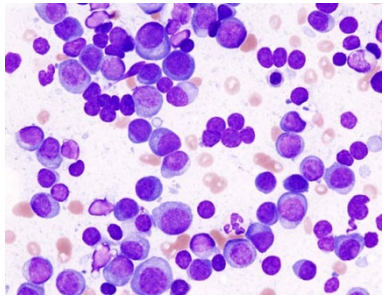
- Physical symptoms: fatigue and bone pain
- Laboratory analyses (minimum):
  - Serum protein electrophoresis or serum immunofixation with either serum free light chain assay and 24-hour urine study
  - CBC with differential and platelet count
  - Serum calcium
  - Serum creatinine
  - Beta-2 microglobulin and albumin
- Bone marrow biopsy
- Bone survey or whole-body bone scan

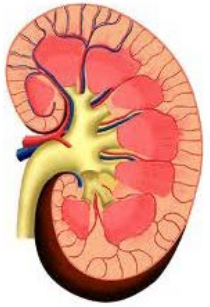
Clinical Manifestations

- Series of genetic mutations, translocations, normal cells turn malignant
- Hallmarks of myeloma: CRAB or myeloma defining events (MDE)

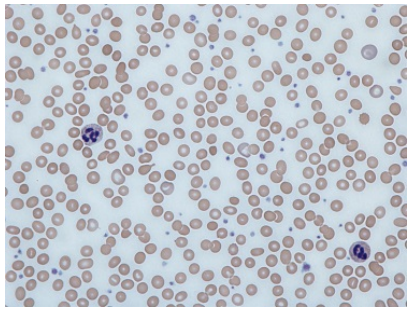


C = Hypercalcemia





R = Renal Complications

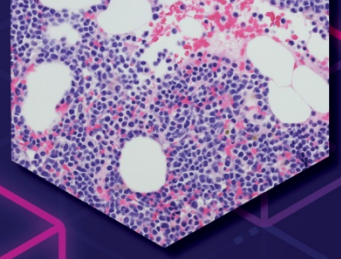


A = Anemia

B = Bone Disease

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. *Lancet Oncol*. 2014;15(12):e538-48.

Updated Criteria from IMWG



MGUS

- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

Smoldering Myeloma

- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% to 60%
- No myeloma defining events

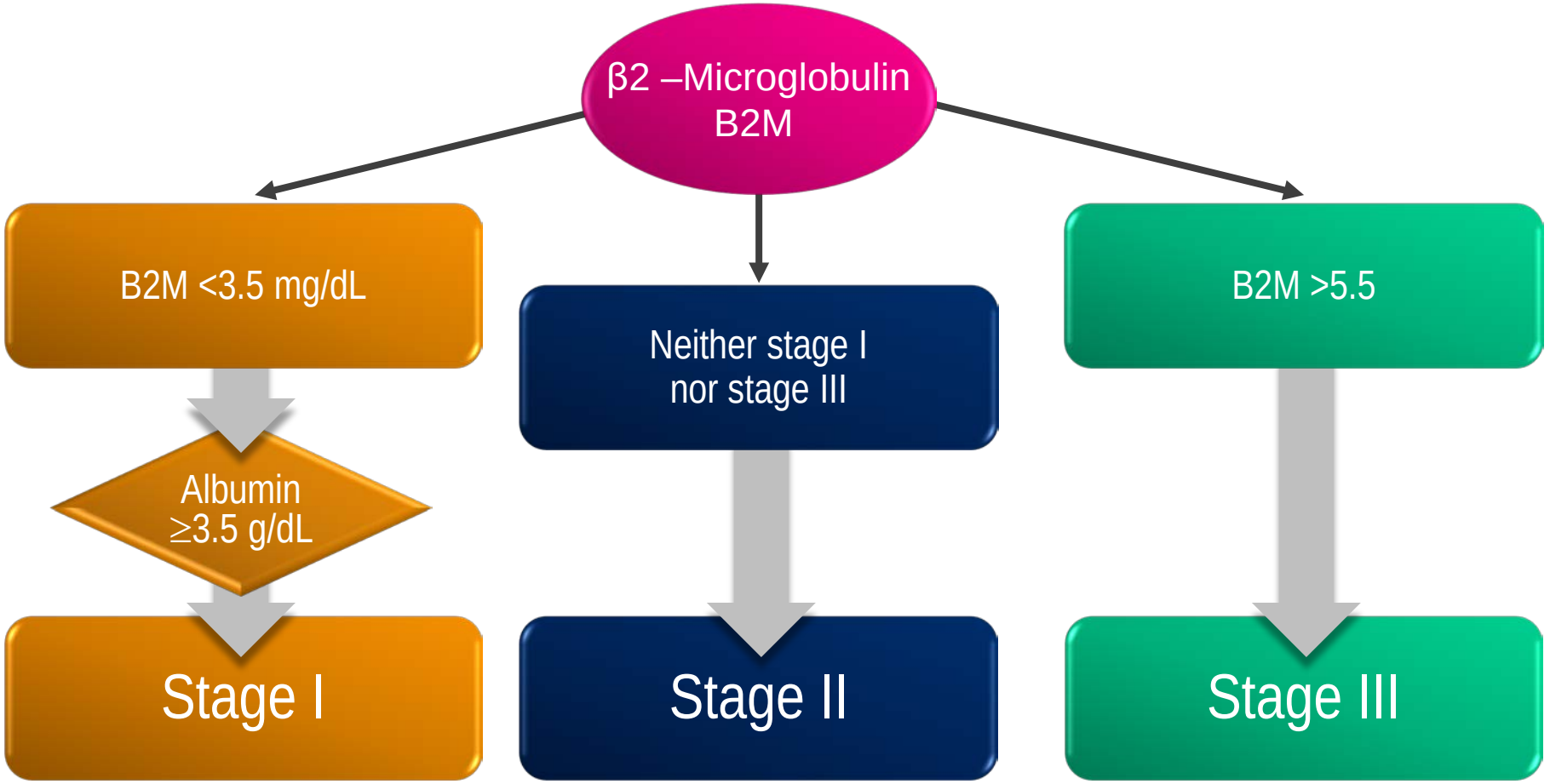
Multiple Myeloma

- Underlying plasma cell proliferation disorder
- AND 1 or more myeloma defining events
- ≥ 1 CRAB* feature
- Clonal plasma cells in BM ≥ 60%
- Serum free light chain ratio ≥ 100
- > 1 MRI focal lesion

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

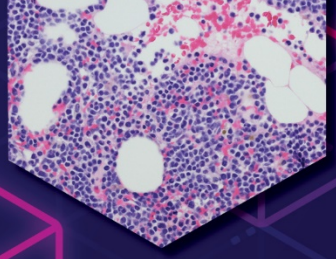
Rajkumar SV, Dimopoulos MA, Palumbo A, et al. *Lancet Oncol*. 2014;15(12):e538-48.

Multiple Myeloma Staging



Greipp PR et al. *J Clin Oncol*. 2005;23:3412.

Revised International Staging System

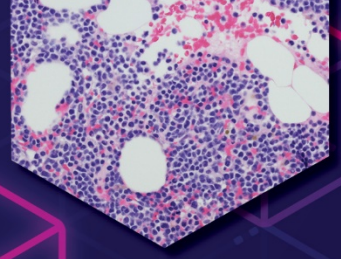


Prognostic Factor	Stage I	Stage II	Stage III
ISS Stage • I - Serum β2-microglobulin<3.5 mg/L, serum **albumin ≥3.5 g/dL** • II - Not ISS stage I or III • III – **Serum 2 microglobulin ≥5.5 mg/L**	ISS Stage I	ISS Stage II	ISS Stage III
AND/OR	AND	Not R-ISS Stage I or III	AND
LDH Normal Serum LDH: < the upper limit of normal High Serum LDH: > the upper limit of normal	Normal		High
AND/OR	AND		AND/OR
Cytogenetic* High Risk: • del(17p) • t(4;14) • t(14;16) Standard risk No high-risk CA	No High Risk		High Risk

CA=chromosomal abnormalities; ISS=International Staging System; LDH=lactate dehydrogenase; MM=multiple myeloma

Based on Updated mSMART Consensus Guidelines 2013. Mikhael JR, Dingli D, Roy V, et al. *Mayo Clin Proc*. 2013;88(4):360-76.

How Aggressive Is My Myeloma?



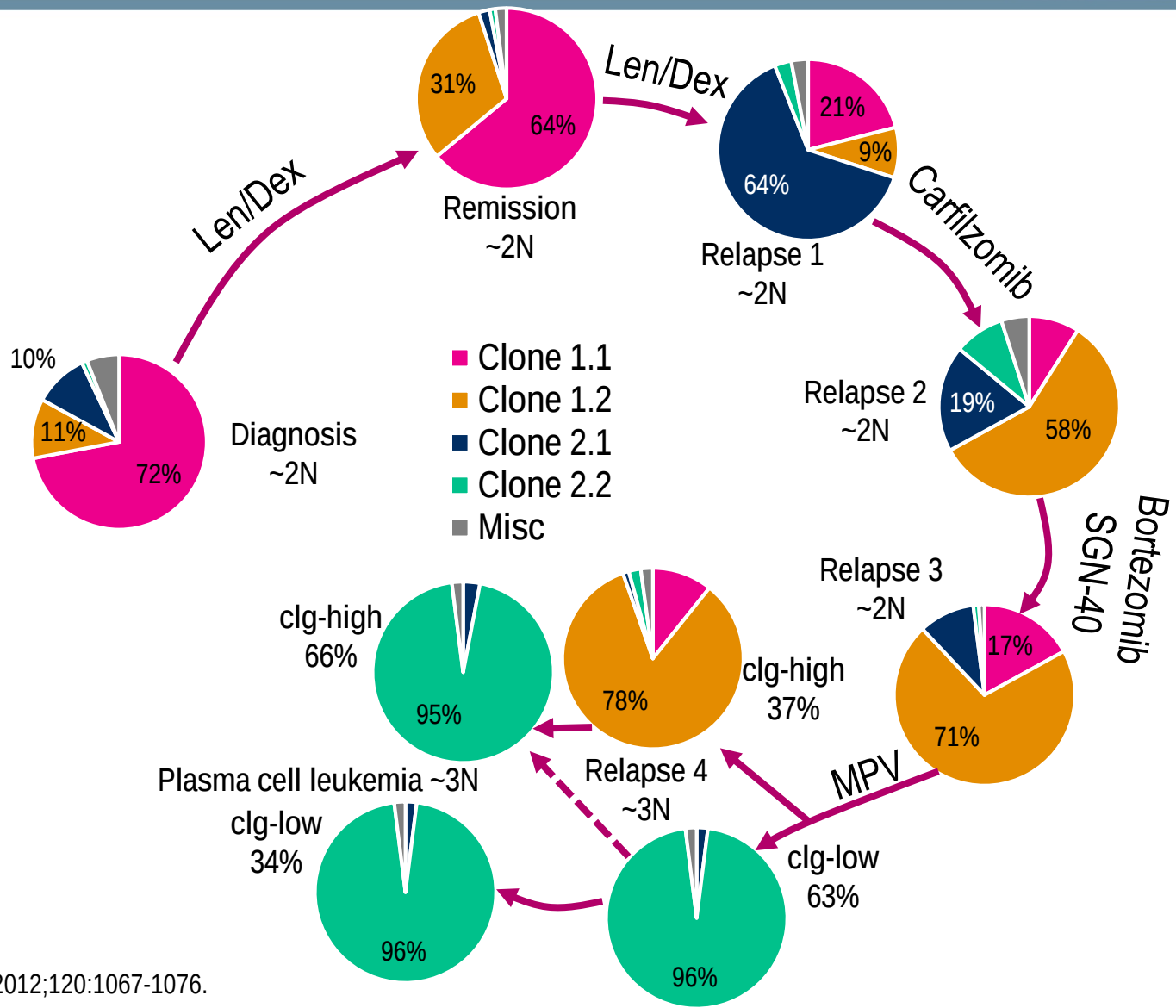
- Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) 3.0: Classification of Active MM

High-Risk	Standard-Risk

▪ FISH
  ▪ del 17p
  ▪ t(4;14)*
  ▪ t(14;16)
  ▪ t(14;20)
  ▪ P53 mutation
  ▪ Gain 1q
▪ RISS Stage 3
▪ High Plasma Cell S-phase
▪ GEP-High-risk signature
▪ Double hit myeloma
▪ Triple hit myeloma
	All others, including:
	  ▪ Trisomies
	  ▪ t(11;14)
	  ▪ t(6;14)

Palumbo A, Avet-loiseau H, Oliva S, et al. *J Clin Oncol*. 2015;33(26):2863-9.

Clonal Evolution and Clonal Competition



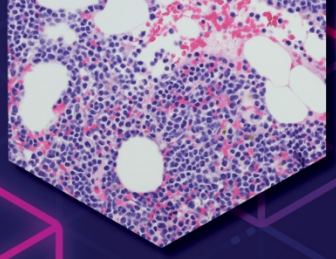
- Multiple clones may be present at the time of diagnosis.
- The predominant clone may change over time, especially after treatment rounds
- Hypothesis: effective treatment reduces or eliminates the dominant clone; however, other clones can still exist

Relapse can occur when:

- Existing clone no longer has to compete for space with the formerly dominant clone
- Acquires additional mutation(s) providing a growth and/or survival advantage

Keats JJ, et al. *Blood.* 2012;120:1067-1076.

Measuring Response to Therapy



Response Type	Abbreviation	Tests						
		M-Protein Reduction		Immunofixation	Bone Marrow			Freelite
		Blood	Urine		PC	Immuno-fluorescence	Other	
Complete response	CR	0	0	Negative	<5%	—	—	—
Stringent complete response	sCR	0	0	Negative	<5%	Negative	—	Normal
Very good partial response	VGPR	>90%	<100 mg/24 hrs	—	—	—	—	—
Partial response	PR	>50%	>90%	—	—	—	—	—
Stable response	SD	Does not meet criteria for response or progressive disease						
Progressive disease	PD	An increase of 25% in M-protein; an increase of 10% in bone marrow plasma cells						

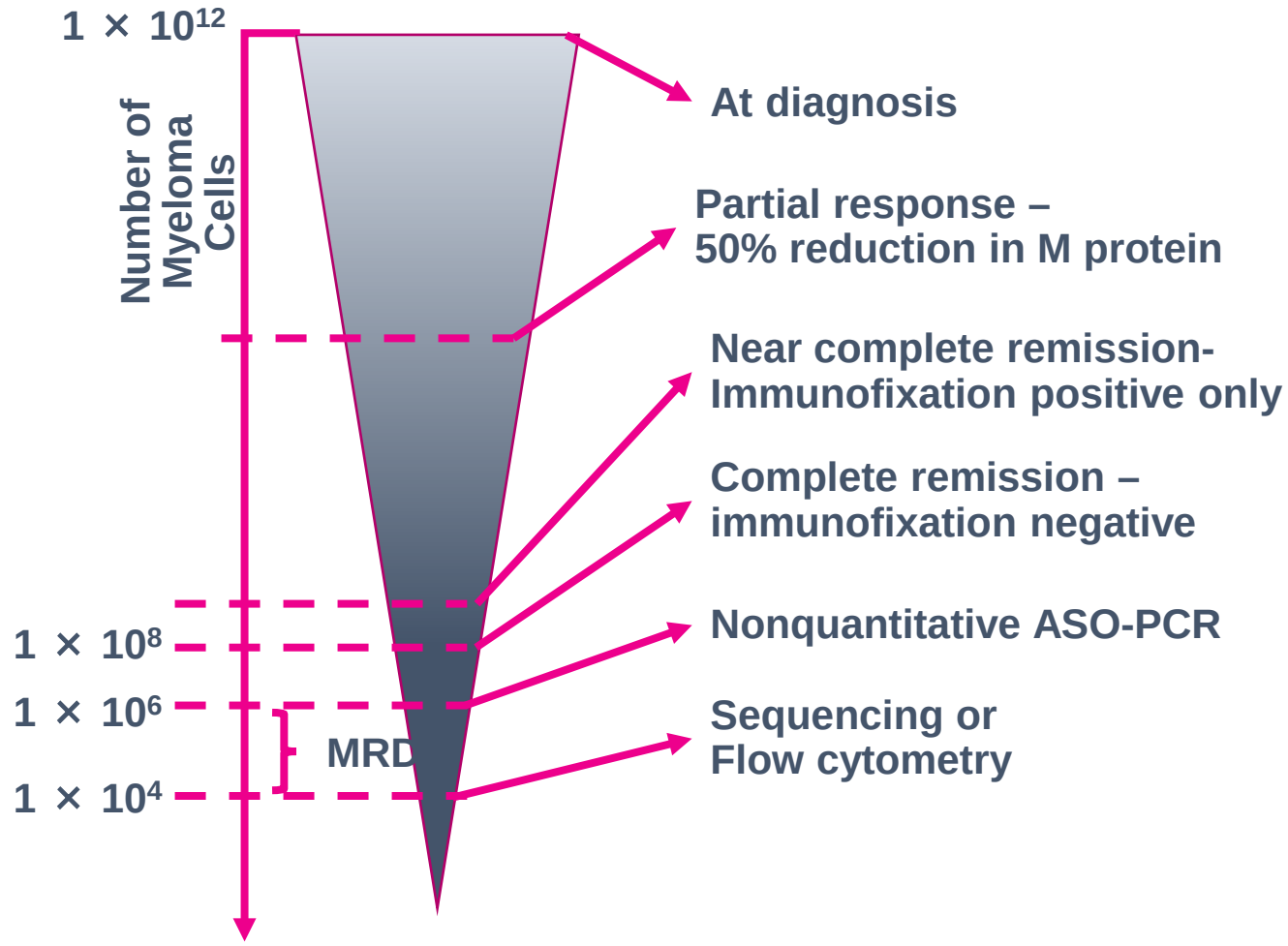
Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a complete response (CR).

Kumar S, Paiva B, Anderson KC, et al. *Lancet Oncol*. 2016;17(8):e328-e346.

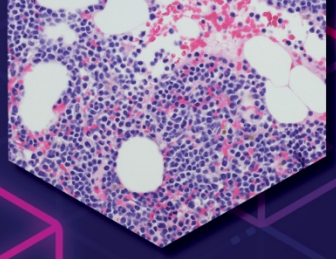
Testing for Minimal Residual Disease (MRD): An Emerging Approach

- Small amounts of myeloma cells despite CR (as measured by standard tests)
- Patients who are MRD negative may have better outcomes
- More-sensitive tests/newer technologies to detect and monitor MRD are now available
  - Flow cytometry
  - Molecular tests
    - Polymerase chain reaction (PCR)
    - Sequenta ClonoSIGHT*: novel, highly sensitive test

Talk to your doctor about types of tests available in your area.



Including Minimal Residual Disease as Response Criteria in Clinical Trial

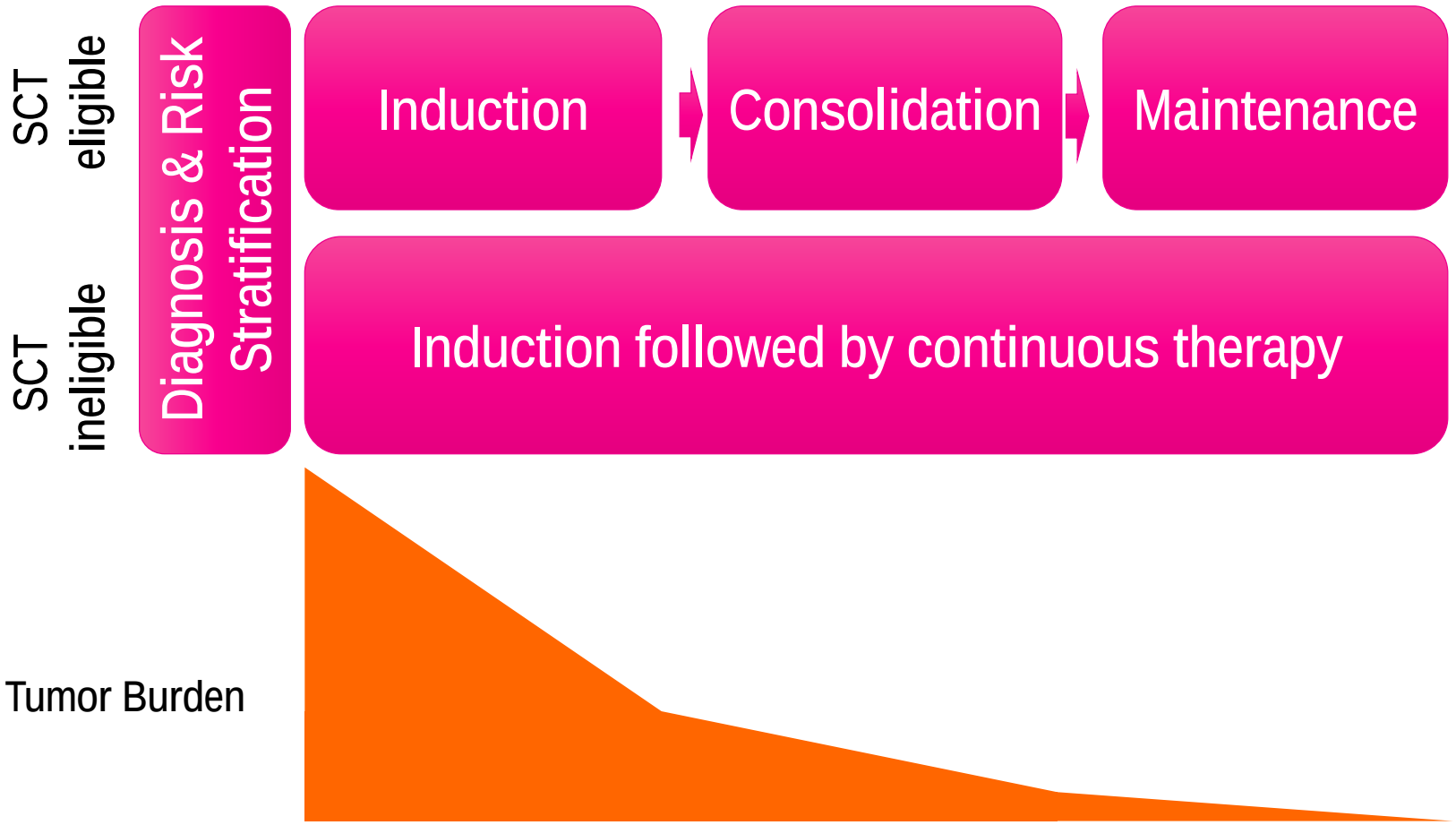


Response subcategory		Response criteria [1]
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD negative	MRD negative in the marrow (next generation flow or next generation sequencing) and by imaging as defined below, confirmed one year apart.[2] Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHTt® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[5] or higher
	Imaging MRD-negative	MRD negative as defined by next generation flow or next generation sequencing PLUS Disappearance of every area of increased tracer intake found at baseline or a preceding PET/CT[3]

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a complete response (CR).

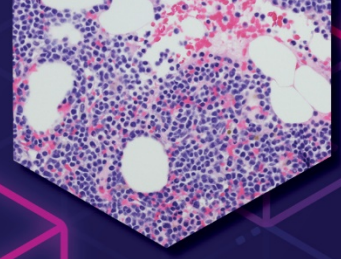
Kumar S, Paiva B, Anderson KC, et al. *Lancet Onco*l. 2016;17(8):e328-e346.

MM Treatment Paradigm



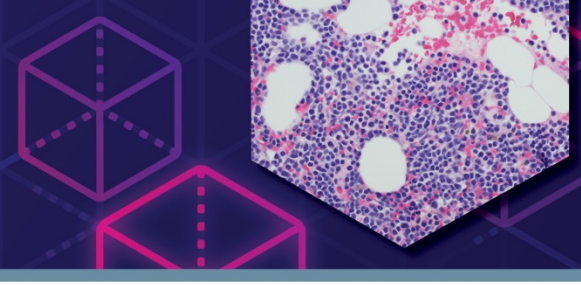
SCT=stem cell transplant

NCCN Treatment Guidelines



	Preferred Therapies		
	Primary Regimens	**Next Steps**	**Supportive Care**
Transplant Eligible	• Bortezomib/lenalidomide/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone *Avoid myelotoxic agents*	Tandem SCT Single Autologous SCT Allogeneic SCT Maintenance with lenalidomide	As needed throughout treatment for all patients: Bisphosphonates or denosumab Orthopedic care
Transplant Ineligible	• Bortezomib/lenalidomide/dexamethasone • Lenalidomide/low-dose dexamethasone • Daratumumab/bortezomib/melphalan/prednisone • Bortezomib/cyclophosphamide/dexamethasone (renal insufficiency)	Lenalidomide maintenance	Radiotherapy Plasmapheresis Erythropoietin IG therapy Pneumococcal vaccine
Relapsed/ Refractory	• Bortezomib/lenalidomide/dexamethasone • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Elotuzumab/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone	Consider second SCT in eligible patients	Herpes zoster, antifungal, PJP prophylaxis Aspirin Ongoing renal care

KRd vs KCd: Phase 2 FORTE (NDMM)



474 NDMM patients ≤65 stratified by age and ISS, randomized 1:1:1

Carfilzomib/cyclophosphamide/dexamethasone (KCd) **for 4** 28-day cycles, then Mel 200-ASCT, consolidation w/ 4 cycles KCd

Carfilzomib/lenalidomide/dexamethasone (KRd) **for 4** 28-day cycles, then Mel 200-ASCT, consolidation w/ 4 cycles KRd

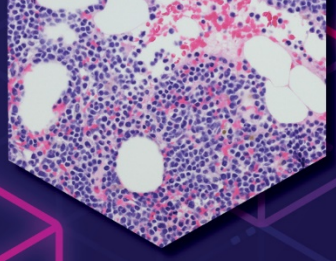
Carfilzomib/lenalidomide/dexamethasone (KRd) 12 28 day cycles

Treatment continued until disease progression or unacceptable toxicity

- **Primary endpoint:** Very good partial response (VGPR) rates

Gay FM, Foa R, Musto P, Cerrato C, Gamberi B, Zamagni E. *J Clin Oncol. 2018;*36(suppl 15):8009.

KRd vs KCd: Phase 2 FORTE (NDMM)



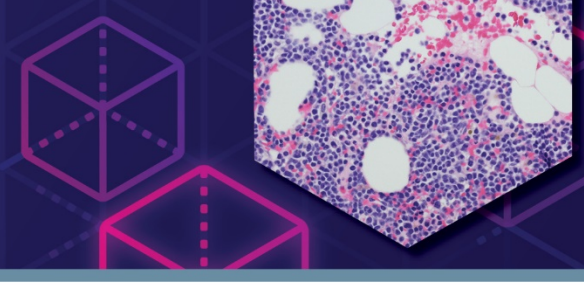
	Overall KCd	Overall KRd	High Risk (FISH) KCd	High Risk (FISH) KRd	R-ISS 2-3 KCd	R-ISS2-3 KRd
Response	N=159	N=315	N=43	N=79	N=91	N=173
≥nCR	21%	33%	12%	30%	13%	29%
≥VGPR	60%	75%	63%	71%	59%	76%
MRD	N=56	N=144	N=14	N=38	N=39	N=88
MRD negative	29%	56%	36%	61%	26%	56%

nCR=near complete response; VGPR=very good partial response, MRD=minimal residual disease

KRd induction significantly improved stringent complete response, complete response, near complete response, very good response rates as well as minimal residual disease negativity vs KCd with similar efficacy in high-risk patients.

Gay FM, Foa R, Musto P, Cerrato C, Gamberi B, Zamagni E. *J Clin Oncol. 2018;*36(suppl 15):8009.

PVd vs Vd: Phase 3 OPTIMISMM Trial (RRMM)



559 R/R patients after ≥ 2 lenalidomide cycles, randomized 1:1

Pomalidomide/bortezomib/low-dose dexamethasone (PVD)
21-day cycles

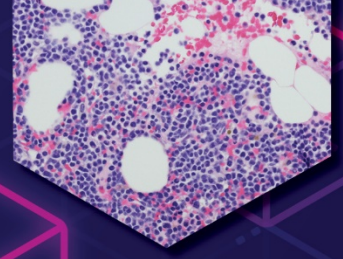
Bortezomib/low-dose dexamethasone (Vd)

Treatment continued until disease progression or unacceptable toxicity

- **Primary endpoint:** Progression-free survival

Richardson PG, Rocafiguera AO, Beksac M, Liberati AM, Galli M, Schjesvold F. *J Clin Oncol. 2018;*36(suppl 15):8001.

PVd vs Vd: Phase 3 OPTIMISMM Trial (RRMM)



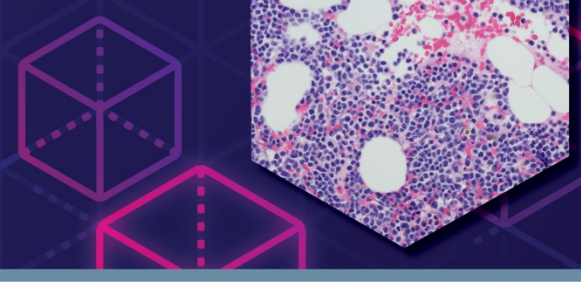
	Intent to Treat PVd, N=281	Intent to Treat Vd, N=278	1 Prior Line of Therapy PVd, N=111	1 Prior Line of Therapy Vd, N=115
Median progression-free survival in months	11.20	7.10	20.73	11.63
Hazard Ratio (95% CI) *P*	0.61 (0.49-0.77) < 0.0001		0.54 (0.36-0.82) 0.0027	
Objective Response Rate **(≥ Partial Response), %**	82.2	50.0	90.1	54.8
≥ Very Good Partial Response	52.7	18.3	61.3	22.6

CI=Confidence Interval

PVd provides a significant and clinically meaningful improvement in progression-free survival in patients with early relapsed/refractory MM, all of whom were lenalidomide exposed and 70% of whom were lenalidomide refractory. PVd also showed benefit in patients with only one prior line of therapy.

Richardson PG, Rocafiguera AO, Beksac M, Liberati AM, Galli M, Schjesvold F. *J Clin Oncol. 2018;*36(suppl 15):8001.

Carfilzomib Dosing: Phase 3 ARROW Study (RRMM)



478 R/R patients with 2-3 prior therapies and prior exposure to proteasome inhibitor and immunomodulatory drug, randomized 1:1

Once-weekly carfilzomib plus dexamethasone (Kd)
Carfilzomib given days 1, 8, 15 of 28-day cycles
Dexamethasone given days 1, 8, 15 all cycles and 22 (only cycles 1-9)

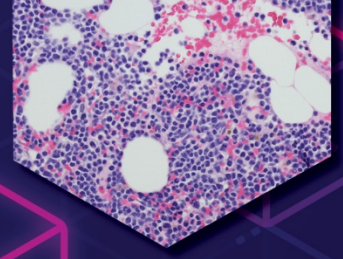
Twice-weekly carfilzomib plus dexamethasone (Kd)
Carfilzomib given days 1, 2, 8, 9, 15 and 16 of 28-day cycles
Dexamethasone given days 1, 8, 15 all cycles and 22 (only cycles 1-9)

Treatment continued until disease progression or unacceptable toxicity

- **Primary endpoint:** Progression-free survival
- **Secondary endpoints**: Overall response rate, overall survival, safety and pharmacokinetics

Mateos MV, Moreau P, Berenson JR, Weisel K, Lazzaro A, Song KW. *J Clin Oncol. 2018;*36(suppl 15):8000.

Carfilzomib Dosing: Phase 3 ARROW Study (RRMM)



	Intent to Treat Kd 70mg/m^2 Once per week, N=240	Intent to Treat Kd 54 mg/m^2 Twice per week, N=238
Median progression-free survival in months	11.2	7.6
Hazard Ratio *P*	0.69 0.0014	
Objective Response Rate	62.9%	40.8%
Stringent Complete Response/Complete Response	7.1%	1.7%

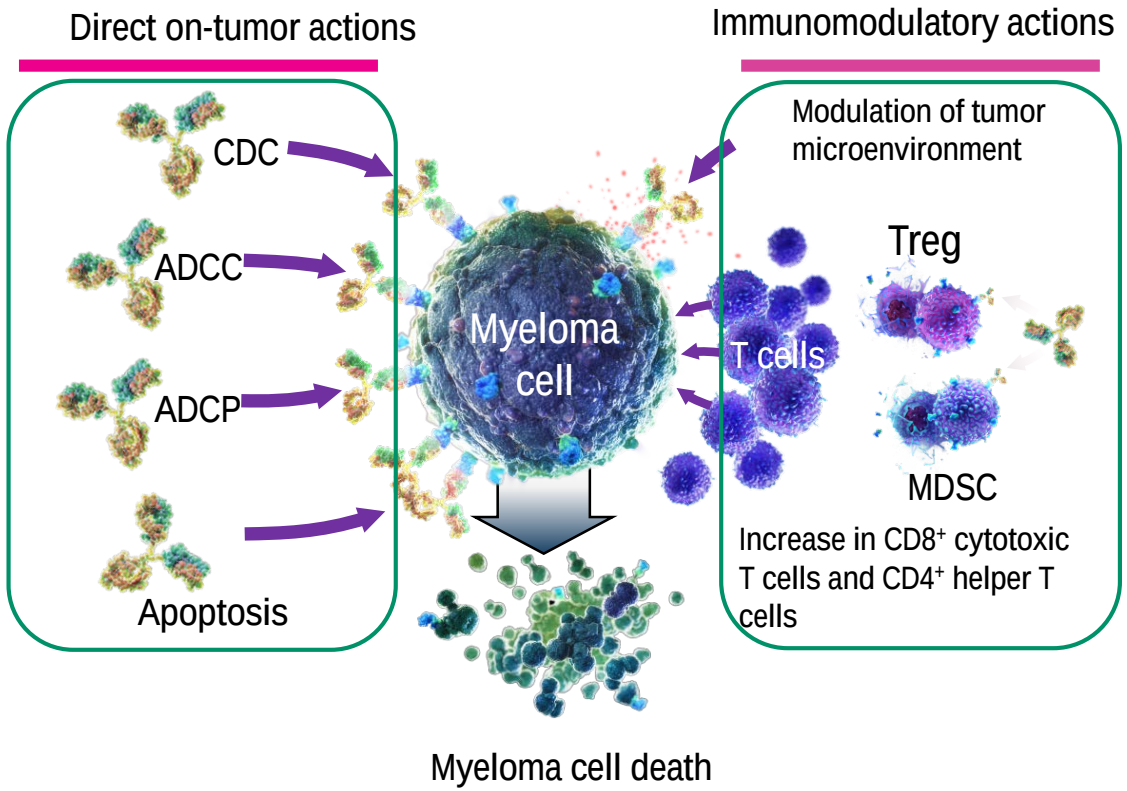
CI=Confidence Interval

Once-weekly Kd administered at 70 mg/m^2 significantly improved progression-free survival and objective response rate compared to 54 mg/ m^2 delivered in two doses with comparable safety.

Mateos MV, Moreau P, Berenson JR, Weisel K, Lazzaro A, Song KW. *J Clin Oncol. 2018;*36(suppl 15):8000.

Daratumumab (DARA)

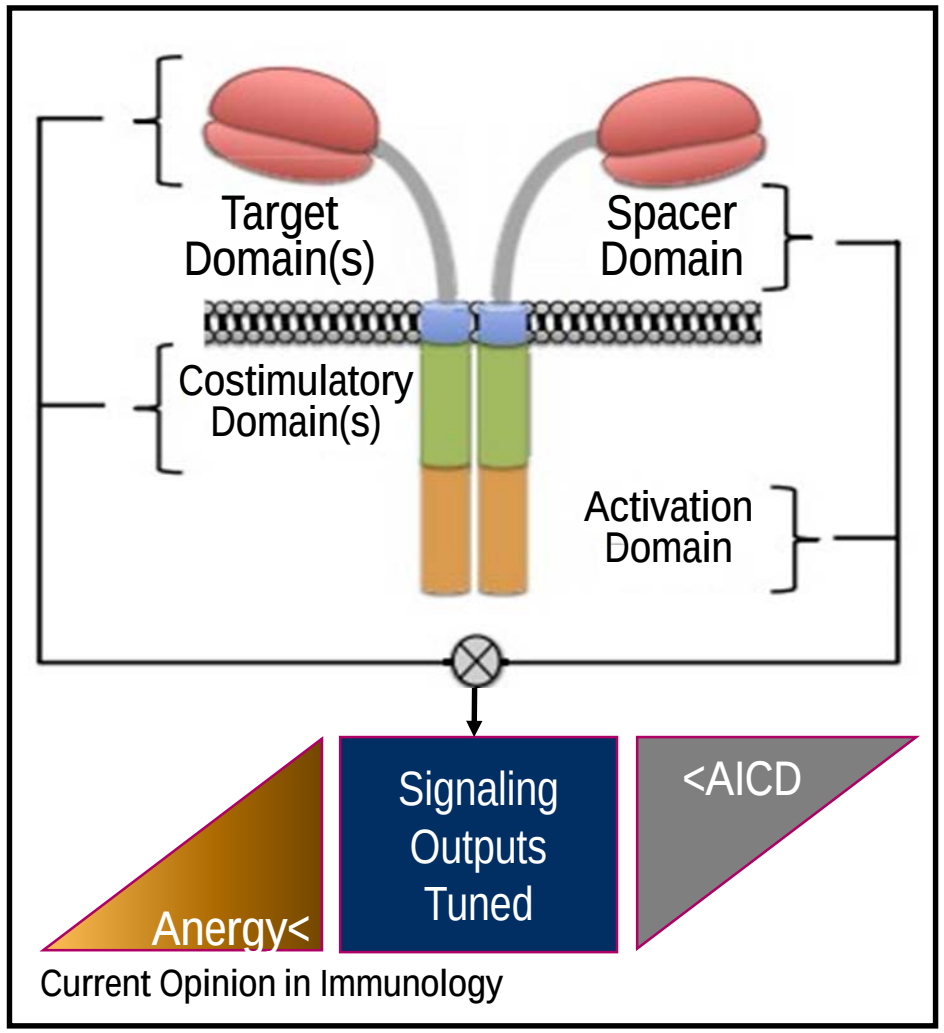
- Human IgGK monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA[1]
- Approved as monotherapy in many countries for heavily pretreated RRMM
- Approved in combination with standard of care regimens in RRMM after ≥1 prior therapy in the US, EU and other countries
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide)in RRMM[2,3]



MoA, mechanism of action; RRMM, relapsed/refractory multiple myeloma; CDC, cellular dependent cytotoxicity; ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; MDSC, myeloid-derived suppressor cell.

1. Touzeau C, Moreau P. *Expert Opin Biol Ther*. 2017;17(7):887-893.\.
2. Mateos MV, et al. Abstract 1150. Oral presentation at: 58th ASH Annual Meeting and Exposition; December 3-6, 2016; San Diego, CA.
3. Usmani SZ, et al. Abstract 1151. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA.

Chimeric antigen receptor T-cell therapy (CAR-T)



CAR-T cells recognize tumor cells independent of their expression of human leukocyte antigen (HLA) molecules, allowing for the elimination of tumor cells that escape conventional T cells by downregulating HLA and/or mutating components of the antigen processing machinery

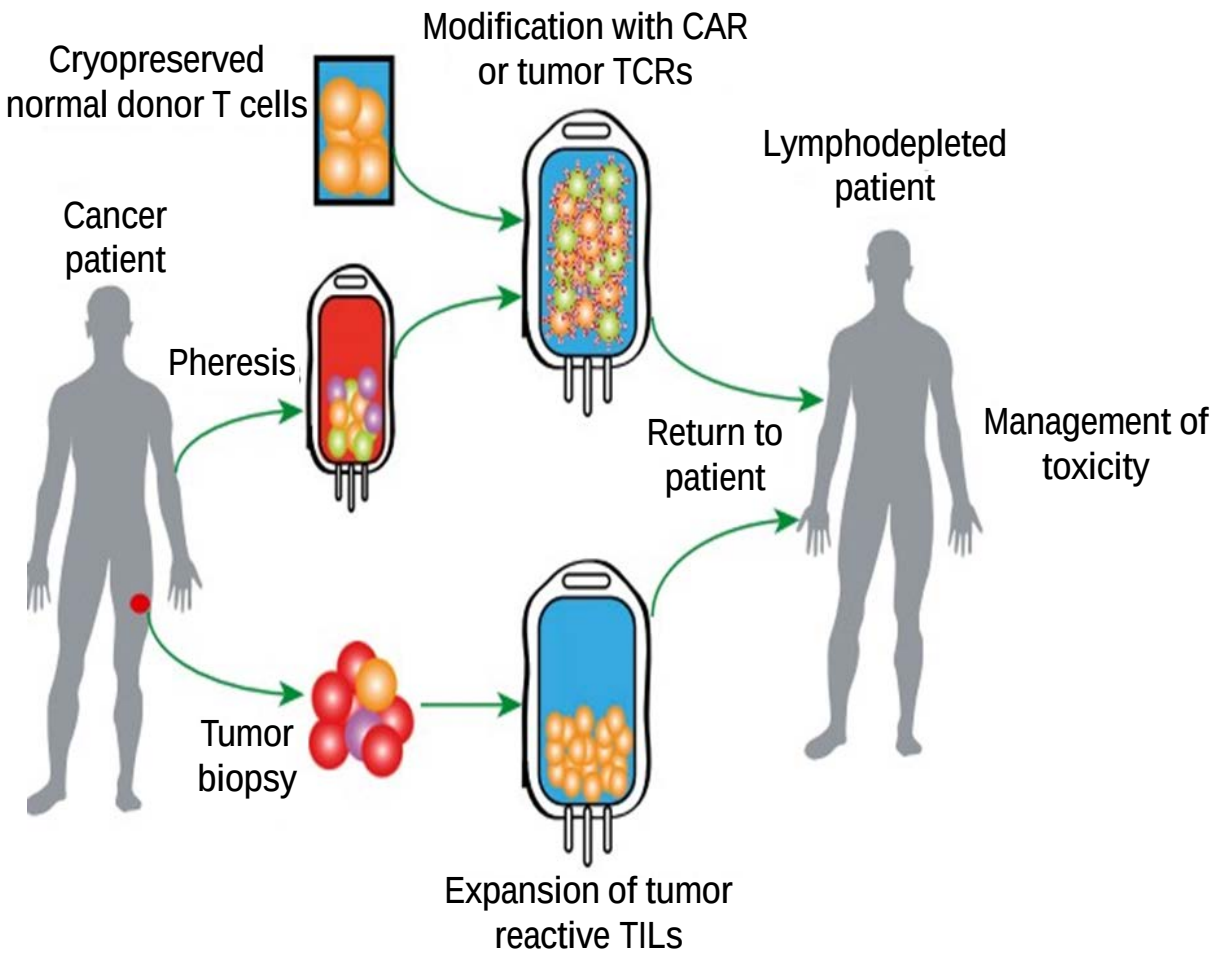
Chimeric antigen receptors (CARs) are fusion molecules typically composed of the following:

- An extracellular single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface molecule on the tumor cell
- A spacer domain that provides flexibility and optimizes T cell and target cell engagement
- A transmembrane domain
- Signaling modules that trigger T cell effector functions

Jensen MC, Riddell SR. *Curr Opin Immunol*. 2015;33:9-15.

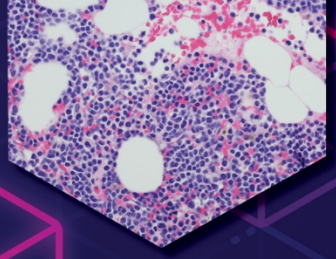
CAR-T Therapy: Pathway to the Patient

- Normal donor cells can be modified to inactivate their alloreactivity while being armed with antitumor CARs or T cell receptors (TCRs)
- Alternatively, a patient's own cells can be modified with antitumor molecules.
- In solid tumors, biopsy specimens can be used to isolate tumor infiltrating lymphocytes (TILs) for expansion
- In most cases, the patient will require some amount of conditioning before receiving antitumor lymphocyte infusions
- Careful management of toxicities emerging from these therapies is also required



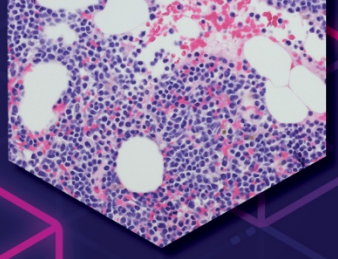
Barrett DM, Grupp SA, June CH. *J Immunol*. 2015;195(3):755-61.

Comparison of BCMA Targeted CAR-T Cells



	Anti-BNMC CAR (16 pts at highest dose)	Bb2121 (22 pts at full dose)	LCAR-B38M (35 pts)	CART-BCMA (24 pts)
Group/Company	NCI	Bluebird/NCI	Nanjing Legend Biotech	Novartis/UPenn (No BCMA expression cut off)
Binder/co-stimulatory signaling	Murine/CD3 & CD28	Murine/CD3 & 4-1-BB	Murine/CD3 & 4-1-BB	Fully human/CD3 & 4-1BB
Transfection	Gamma-retroviral	Lentiviral	Lentiviral	Lentiviral
Lymphodepletion	Flu/CY d-5 to -3	Flu/CY d-5 to -3	CY	None / with CY
Median prior lines of therapy	9.5 (63% Refr)	8 (32% penta refr)	3	9
Reported Efficacy	ORR - 81% VGPR -63% EFS-median 31 wks	ORR – 95.5% mDOR – 10.8 mo 100% MRD neg	15 CRs/13 PRs in 35 19 with longer flu 100% ORR; 74% CR No CR pt relapsed at 6 mo	2 CRs, 3 VGPRs, 6 PRs in 24 patients Only 4 responders progressed at 40 weeks
Safety Data	Substantial but reversible	Manageable CRS	Transient CRS	1 death – progressive disease/candidaemia

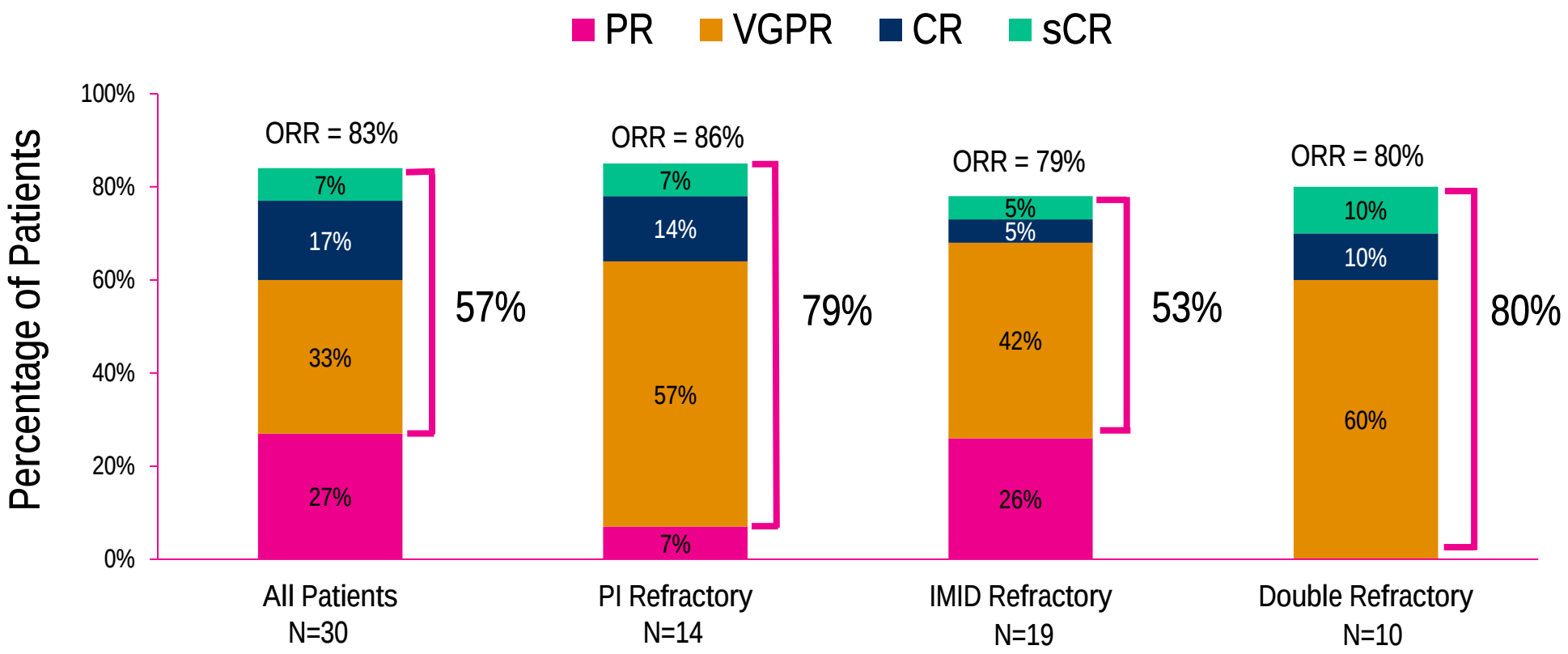
Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with R/R MM



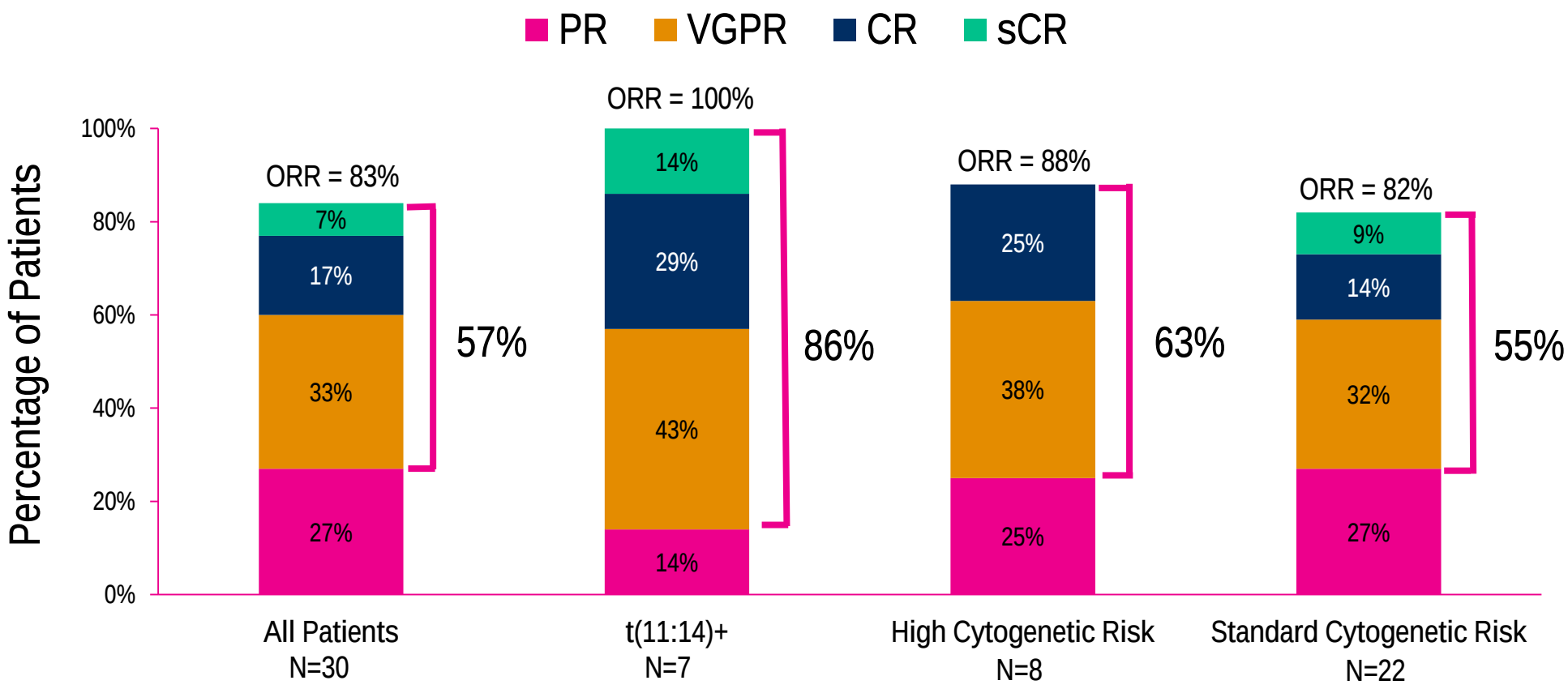
Luciano J. Costa, Edward Allen Stadtmauer, Gareth John Morgan, Gregory P. Monohan, Tibor Kovacsovics, Nicholas Burwick, Andrzej Ja. Jakubowiak, Mehrdad Mobasher, Kevin Freise, Jeremy A. Ross, John Carl Pesko, Wijith Munasinghe, Jaclyn Cordero, Lura Morris, Paulo Cesar Maciag, Orlando Bueno, and Shaji Kumar

*J Clin Oncol. 2018;*36(suppl 15):8004.

Objective Responses in All Patients and Those Refractory to PIs and IMiDs



Objective Responses in Patients Based on Cytogenetic Risk Status



Summary of Safety

Adverse event, n (%)	Any Grade	Grade 3/4
Total	33 (79)	12 (29)
Diarrhea	24 (57)	0
Fatigue	16 (38)	3 (7)
Platelet count decreased	13 (31)	3 (7)
Nausea	12 (29)	1 (2)
Lymphocyte count decreased	9 (21)	6 (14)

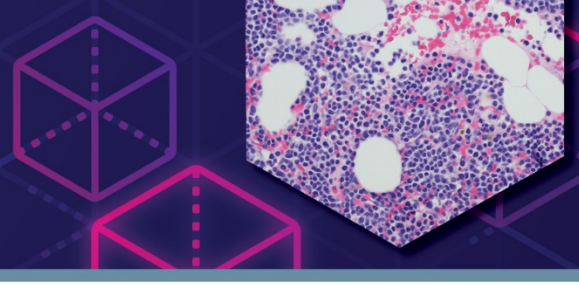
AEs for ≥20% of patients for any grade AE or for ≥10% with grade 3 or 4 AEs

Serious adverse event, n (%)	Total
Any serious event	5 (12)
Acute kidney injury	2 (5)
Influenza	2 (5)
Pneumonia	2 (5)

Serious adverse events in ≥2 patients

- 1 case of laboratory TLS:
  - patient was t(11:14)+
  - hospitalized and received hydration and allopurinol
  - TLS labs resolved and treatment resumed

Summary



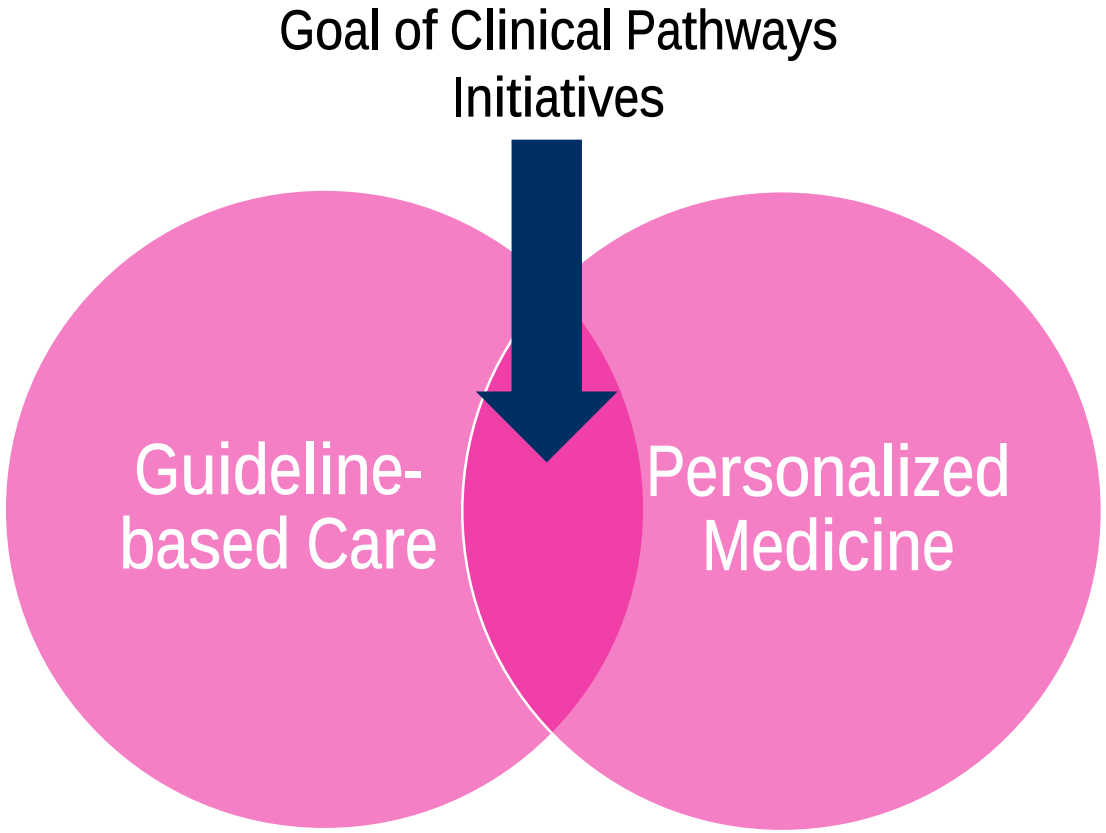
- The management of MM requires a stepwise approach involving the selection of therapy based on initial assessment and risk stratification.
- In the event of nonresponse or relapse, a myriad of treatment options are available to the clinician.
- Emerging data, particularly surrounding targeted therapies and biologics, are regularly reshaping the treatment paradigm and clinical guidelines.
- Immunotherapies based on mechanisms affecting T cell activation and regulation demonstrate promise as the next wave of agents to be potentially added to the treatment armamentarium.

Can Care Pathways Reduce Treatment Variability and Improve Outcomes?

Edmund Pezalla, MD, MPH
Chief Executive Officer
Enlightenment Bioconsult, LLC

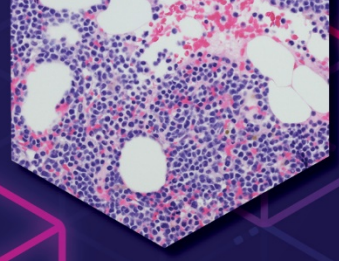
Clinical Pathways Initiatives Aim to Reduce Treatment Variability While Allowing Individualized Care in Oncology

Balancing treatment *standardization* with *personalization* is cited among the top three challenges in cancer care for more than one third of MCOs



The 2016 Genentech Oncology Trend Report. 8th ed. https://www.gpbch.org/docs/2016_genentech_oncology_trend_report.pdf. South San Francisco, CA: Genentech; 2016. Accessed March 2017.

Characteristics of Clinical Pathways Programs



Guide rational therapeutic decisions with evidence-based data

Offer formal structural elements to guide decisions

Often based on National Comprehensive Cancer Network (NCCN) Guidelines

Allow coordination with clinical trials, registries and real-world clinical trials

Improve quality of care and efficiency in resource utilization

Support shared decision-making with patients and permits individualization based on clinical and biological specifics

Balch AJ, et al. Recommendations for the Role of Clinical Pathways in an Era of Personalized Medicine. *AJMC*. April 13, 2016. https://www.ajmc.com/journals/evidence-based-oncology/2016/april-2016/recommendations-for-the-role-of-clinical-pathways-in-an-era-of-personalized-medicine. Accessed September 2018.

Pathways Initiatives Condense an Expansive Menu of Clinical Options into a More Concise, Stepwise Process for Providers

NCCN Clinical Practice Guideline

Example: Previously Treated MM

Preferred Regimens	Other Regimens
• Bortezomib/lenalidomide/dexamethasone • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Elotuzumab/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone **Useful in Certain Circumstances** • Bendamustine • Dexamethasone/cyclophosphamide/etoposide/cisplatin • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide/bortezomib • High-dose cyclophosphamide	• Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib (weekly)/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Bortezomib/dexamethasone • Daratumumab • Daratumumab/pomalidomide/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Ixazomib/dexamethasone • Ixazomib/pomalidomide/dexamethasone • Lenalidomide/dexamethasone • Panobinostat/bortezomib/dexamethasone • Panobinostat/carfilzomib • Panobinostat/lenalidomide/dexamethasone • Pomalidomide/cyclophosphamide/ dexamethasone • Pomalidomide/carfilzomib/dexamethasone

Clinical Pathways Program

Plan-derived Criteria

Plan-derived Criteria

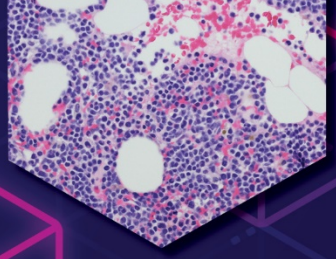
Options for First Relapse

Options for Second Relapse

Options for Salvage

NCCN Guidelines Version 1.2019 Multiple Myeloma.

Best Pathways Address Full Spectrum of Cancer Care



Diagnosis and Evaluation

- Lab testing, genomic profiles, imaging
- Clinical evaluation

Treatment and Surveillance

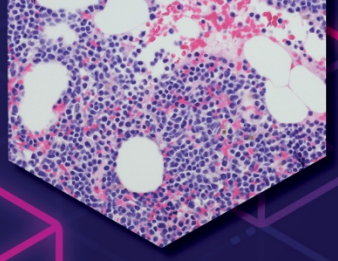
- Drug therapies, sequencing, transplantation, surgery, clinical trials
- Ongoing monitoring, labs and imaging

Survivorship and Palliative care

- Follow-up care
- Palliative and end-of-life care

Zon, R. ASCO Policy Statement on Clinical Pathways in Oncology: Why Now? *AJMC*. April 11, 2016. https://www.ajmc.com/journals/evidence-based-oncology/2016/april-2016/asco-policy-statement-on-clinical-pathways-in-oncology-why-now. Accessed September 2018.

Pathways Programs Address Surveillance, Palliative Care and Supportive Care in MM



BISPHOSPHONATES

Have demonstrated increased survival and decreased bone complications

Medicare costs for bone disease is $25,000

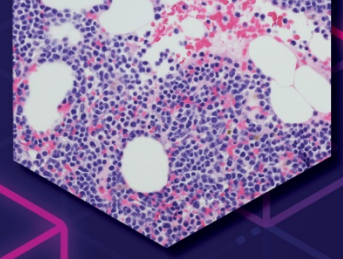
- May significantly save cost by preventing complications

Increased risk of osteonecrosis of the jaw

- Zoledronic acid vs pamidronate?
- Limit use to 18-24 months?
- Could you decrease interval if disease controlled?
- Mandate dental exam BEFORE starting therapy

Schulman KL, Kohles J. *Cancer*. 2007;109(11):2334-42.
Kyle RA, Yee GC, Somerfield MR, et al. *J Clin Oncol*. 2007;25(17):2464-72.
Terpos E, Roodman GD, Dimopoulos MA. *Blood*. 2013;121(17):3325-8.

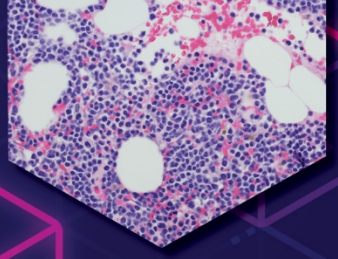
Managed Care Trends



- Guidelines- and pathways-based initiatives are quickly gaining traction:
  - 78% of MCOs use oncology pathways and 35% specify preferred pathway for their network oncologists.
  - 37% of MCOs specify use of NCCN Value Pathways.
  - 48% of MCOs have pathways for multiple myeloma now and 19% report it is a high priority area for pathway development.

2018 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed September 2018.
Greenapple R, *J Oncol Pract*. 2013;9:81-83.

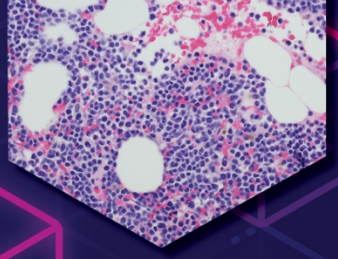
Providers Support Guidelines and Pathways



- Oncologists are rapidly adopting guidelines and pathways, too:
  - Practices report compliance with pathways increased 42% from 2014-2016 and twice as fast 2016-2017.
  - 78% of oncologists used guidelines in 2017, up from 53% in 2016.
  - 52% of oncologists use pathways, up from 45% the previous year.
  - Increasingly, practicing oncologists play a central role in pathway development.

ASCO State of Cancer Care in America 2017.
2018 Oncology Trend Report. https://www.genentech-forum.com/oncology-trends.html. Accessed September 2018.
Greenapple R, *J Oncol Pract*. 2013;9:81-83.

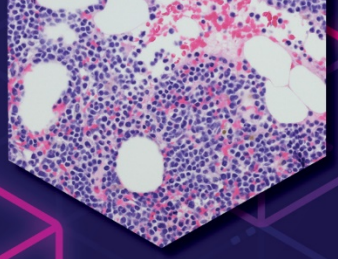
ASCO Policy Statement on Clinical Pathways in Oncology



RECOMMENDATIONS

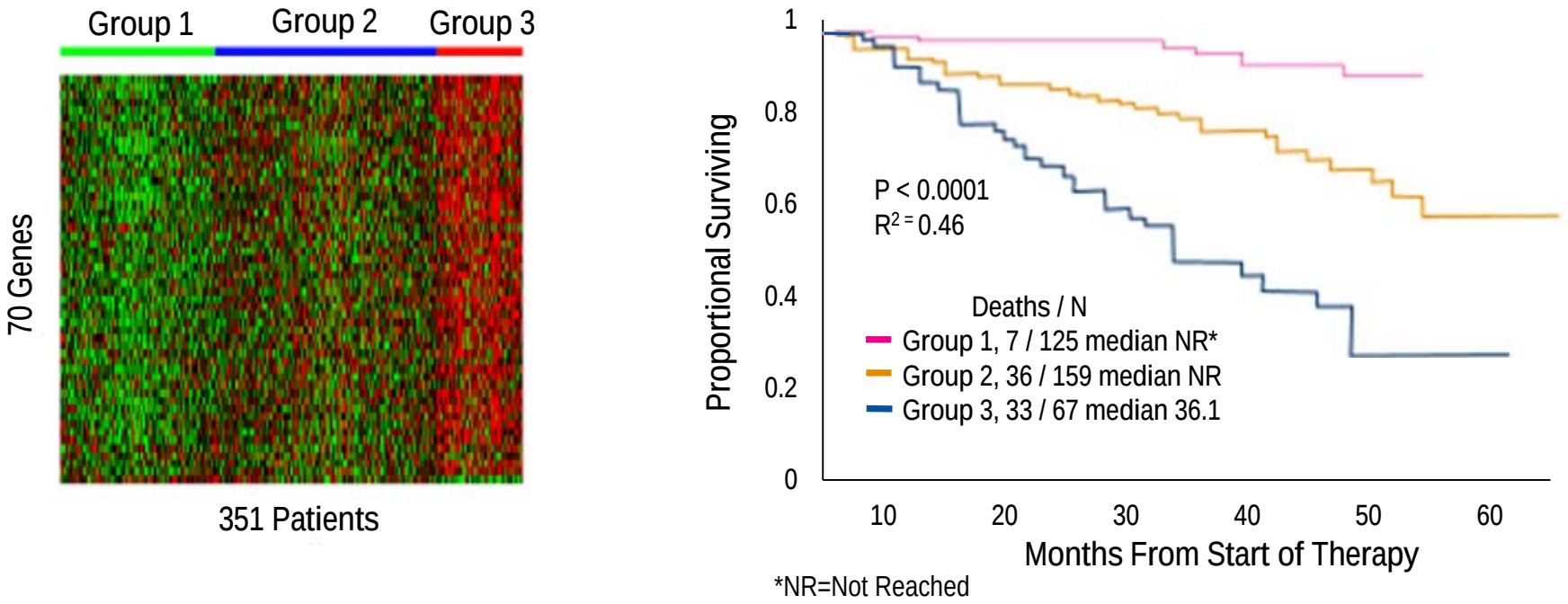
1) A collaborative, national approach is necessary to remove the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways.
2) Oncology pathways should be developed through a process that is consistent and transparent to all stakeholders.
3) Oncology pathways should address the full spectrum of cancer care, from diagnostic evaluation through medical, surgical and radiation treatments, and include imaging, laboratory testing, survivorship, and end-of-life care.
4) Oncology pathways should promote the best possible evidence-based care in a manner that is updated continuously to reflect the rapid development of new scientific knowledge, as well as insights gained from clinical experience and patient outcomes.

ASCO Policy Statement on Clinical Pathways in Oncology (continued)



5) Oncology pathways should recognize patient variability and autonomy and stakeholders must recognize that 100% concordance with oncology pathways is unreasonable, undesirable, and potentially unsafe.
6) Oncology pathways should be implemented in ways that promote administrative efficiencies for both oncology providers and payers.
7) Oncology pathways should promote education, research, and access to clinical trials.
8) Robust criteria must be developed to support certification of oncology pathway programs. Pathway programs should be required to qualify based on these criteria and payers should accept all oncology pathway programs that achieve certification through such a process.
9) Pathway developers, users, and private and governmental funding agencies should support research to understand pathway impact on care and outcomes.

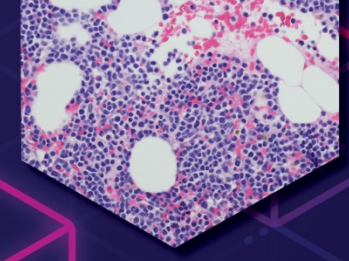
Pathways in MM Must Ultimately Be Capable of Allowing Personalized Treatment Plans



Overall survival of MM patients from the start of therapy based on 70 highly overexpressed or underexpressed genes distinguished 3 groups of patients; good, intermediate, or poor prognosis

Shaughnessy JD, Zhan F, Burington BE, et al. *Blood*. 2007;109(6):2276-84.

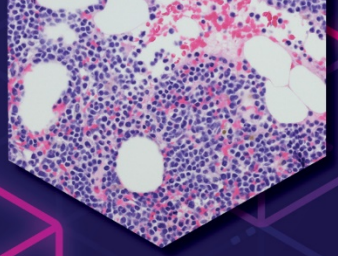
Common Incentives for Provider Participation in Pathways Programs



- Giving oncologist a share of the cost savings – 44%
- Improved/higher drug reimbursement for oncologist – 36%
- Improved/higher evaluation and management reimbursements – 36%
- Reductions in PA or precertification requirements – 24%
- Faster processing of PAs/precertifications – 24%
- Preferred provider status within the network – 24%
- Expedited UM reviews and reimbursement processing – 20%

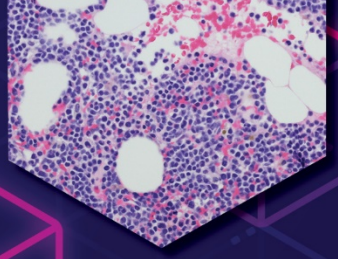
The 2016 Genentech Oncology Trend Report. 8th ed. https://www.gpbch.org/docs/2016_genentech_oncology_trend_report.pdf. South San Francisco, CA: Genentech; 2016. Accessed March 2017.

Potential Applications for Pathways in MM



- Criteria for transplant vs drug therapy
- Drug therapy selection
- First-line preferred therapies, subsequent sequencing
- Maintenance therapy
- Relapsed/refractory disease

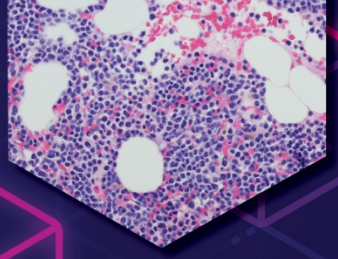
Results from Integrating Pathways with Utilization Management



- US Oncology Network:
  - Adopting pathway-directed care for non-small cell lung cancer reduced one-year cost of outpatient treatment from $28,000 to $18,000 (35%).
  - No difference detected in overall survival.
- UPMC:
  - Multiple courses of radiation therapy for bone metastases was 95% in 2003.
  - Research showed a single course as effective and associated with fewer adverse effects.
  - Pathway adopted new recommendation for single treatment radiation therapy, 10 or more considered off-pathway.
  - Rate of single treatment use doubled 2003-2014. By 2014, 90% used fewer than 10 treatments.

Clinical Pathways based on latest clinical evidence can influence patterns of care for bone metastases. UPMC website. https://www.astro.org/uploadedFiles/Main_Site/News_and_Media/Media_Resources/Press_Kits/Annual_Meeting_2015/GebhardtASTRO2015.pdf. Published October 20, 2015. Accessed October 2018.

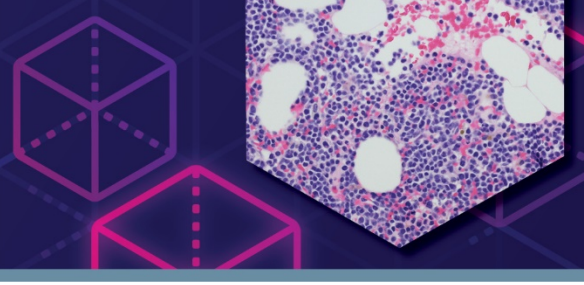
Results from Integrating Pathways with Utilization Management (continued)



- Via Pathways:
  - Changed pathways for metastatic colorectal cancer used at UPMC and Indiana University Health in August 2014.
  - Phase III study showed panitumumab ($37,827 per 16-week course) as effective as cetuximab ($44,303 per 16-week course) for patient with KRAS-WT metastatic disease.
  - No consequence for providers for deviation from pathway; no restrictions on cetuximab.
  - Prescribing rapidly changed from 93.5% cetuximab and 6.5% panitumumab to 18.1% cetuximab and 81.9% panitumumab.
  - Annual savings in first year exceeded $711,000.
- Mercy
  - Reported $10 million in savings associated with pathways in 2015.
  - Increased savings to $14 million in 2016.

Ellis PG, O'neil BH, Earle MF, et al. *J Oncol Pract*. 2017;13(5):e522-e529.
Wright U. Mercy Clinical Pathway: Improving Quality and Cost. Oral presentation at: HIMSS 2017; February 20, 2017; Orlando.

Summary

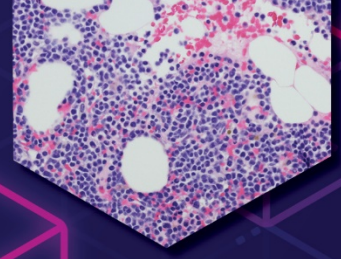


- Optimally, pathways balance care standardization based on national guidelines with personalization based on patient characteristics.
- Both MCOs and oncologists increasingly use pathways to guide treatment as options expand.
- Pathways should address full cycle of care from diagnosis and evaluation through sequential treatment and follow up as well as survivorship or palliative care.
- Pathway development should be transparent, involve oncologists and provide patient-centered care.
- Pathways should be updated frequently to reflect new therapeutic developments and guidelines.
- Effective pathways save money while providing quality care.

Managed Care and Specialty Pharmacy Management Approaches to Enhance Quality and Mitigate the Cost of Care

Vanita Pindolia, PharmD, BCPS, MBA
Vice President, Ambulatory Clinical Pharmacy Programs
Henry Ford Health System

Current Trends in Oncology



Targeted therapy, multidrug regimens and increased survivorship contribute to dramatic rise in costs.

Many cancers, particularly hematologic malignancies, now treated as chronic diseases.

Medicare is the largest growing patient sector in US

- Baby Boomers reaching age of 65 years
- Elderly at highest risk for cancer
- Demand for greater number of oncology practices

Demand for greater number of oncology services needed for precision medicine and improved patient care is leading to oncology practices conglomerating and being purchased by health systems.

Chart Source: 2016 Community Oncology Alliance Practice Impact Report.

Current Trends in Oncology Medications

- 73 new cancer therapies approved or indications expanded since 2012.
- 16 new cancer drugs approved in 2017, all targeted therapies.
- Global spending on cancer medications rose from $96 billion in 2013 to $133 billion in 2017.
  - US led the trend with highest spend: 33% (2013) to 50% (2017) of global spend
- US cancer drugs expected to cost $100 billion by 2022.
- Median annual cost of new cancer drug doubled in last decade from $75,000 to $150,000.
- 87% of cancer drugs are used by fewer than 10,000 patients each year.
- 700 new molecules in late-stage development now.

New Cancer Therapies Approved/Indications Expanded

2013	2014	2015	2016	2017	2018
12	10	21	11	16	3

Total US Spending Oncology Therapeutic Medicines, 2013-2017

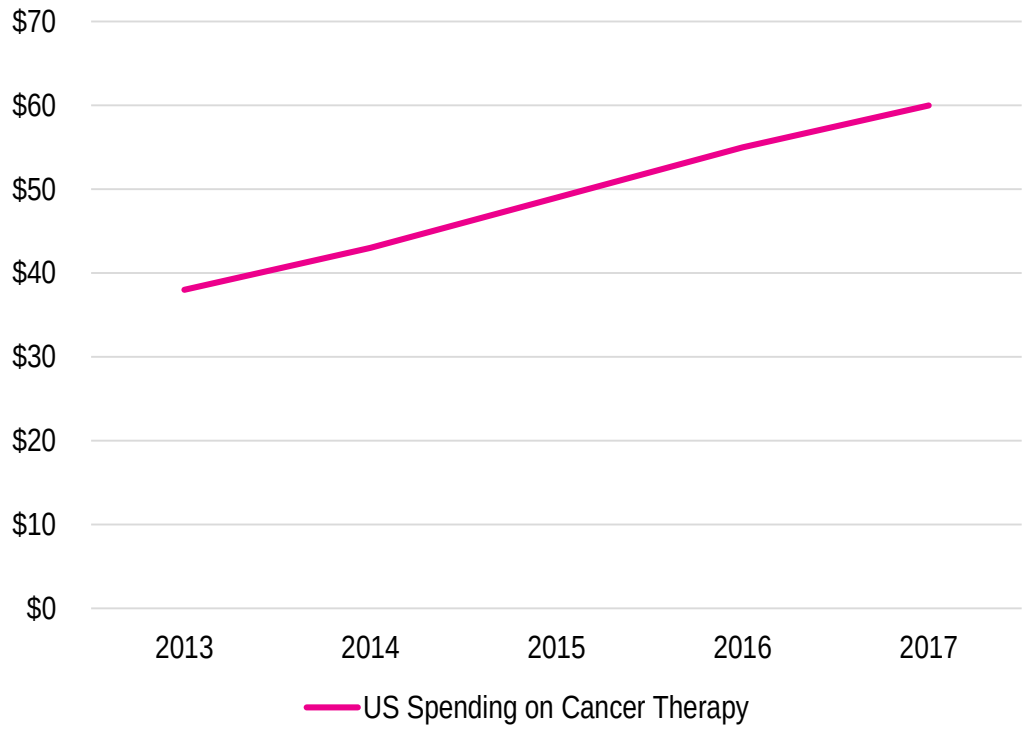
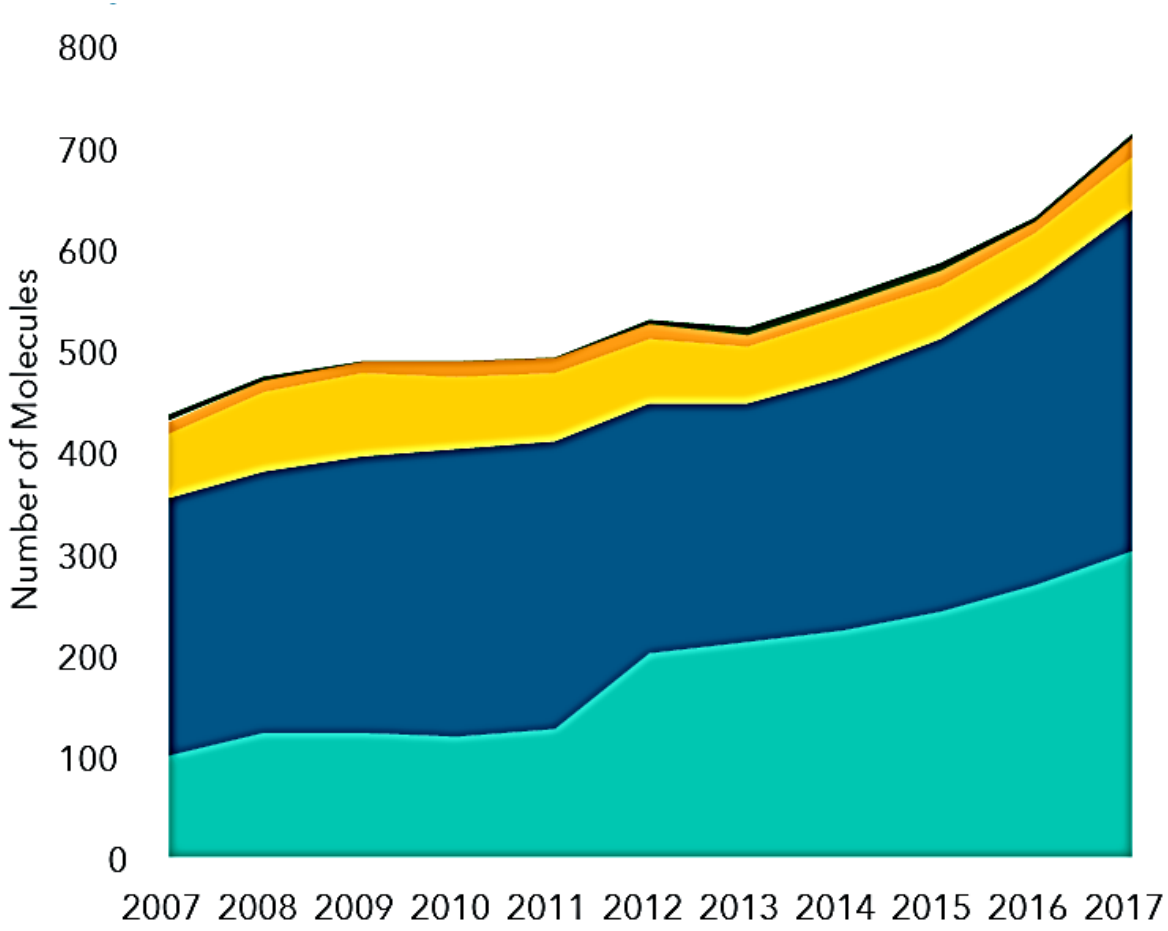


Chart Source: IQVIA, ARK R&D Intelligence, Dec 2017

Global Oncology Trends 2018. IQVIA website. Published May 24, 2018. Accessed October 2018.
FDA Approved Drugs for Oncology. CenterWatch website. https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology. Accessed October 2018.

Increasingly Targeted Agents Being Developed

The Pipeline of Late Phase Oncology Molecules, 2007-2017

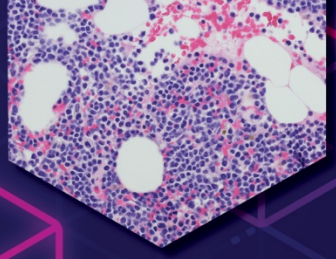


Year	2007 (434)	2017 (710)
Radiotherapies	0.9% (4)	0.4% (3)
Hormonals	3% (14)	2% (17)
Cytotoxics	15% (63)	8% (54)
Targeted Small Molecule	59% (254)	47% (335)
Targeted Biologics	23% (99)	42% (301)

Innovative Payer Oncology Models Require Multiple Approaches

Benefit Design (Cost Share) & Formulary

Transforming Utilization Management



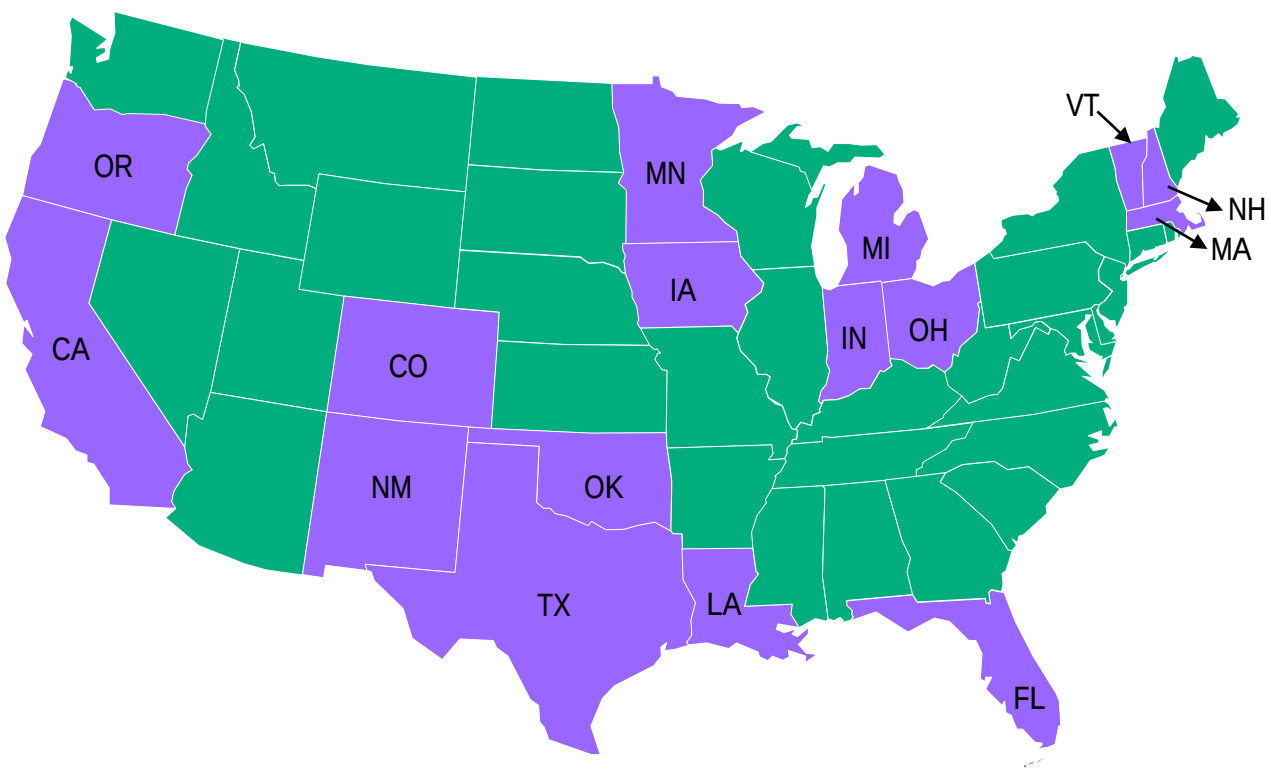
- Reduce cost and utilization management inefficiencies, increase value.
- Patient lobbying and physician burden are leading to increased transparency in utilization management outcomes.
- Each pre-authorization costs payers and providers $50-$100.
- Methods to decrease unnecessary UM activities:
  - Automate authorizations in workflow
  - Limit prior authorization to drugs not in national guideline/pathway
  - Limit drug therapy choice in disease states where multiple options targeting same oncogene/tumor suppressor gene are available
  - Link EHRs to medical review to streamline authorizations
  - Track trends in authorization and utilization in aggregate and by provider
  - Refine and update
    - Reflect current guidelines for care
    - Monitor provider outliers

Mehrabian N. Reinventing Utilization Management (UM) to Bring Value to the Point of Care. *Healthcare IT News*. https://www.healthcareitnews.com/news/reinventing-utilization-management-um-bring-value-point-care. September 18, 2107.

Evolving Restrictions on Established Utilization Management Processes

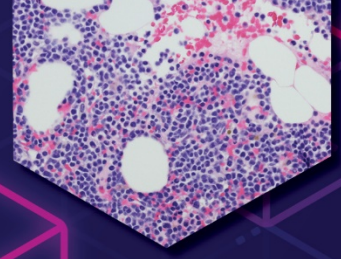
- 16 states require all health plans to use a common electronic prior authorization form.
- Several states set time limits for prior authorization approvals.
- At least 18 states require exceptions to step therapy, specify time limits to respond to override requests or limit time step therapy can be mandated.
- Some states prohibit use of step therapy for patients who have gone through it previously with another health plan.

States Requiring Common Electronic Prior Authorization Form



Ollove M. States Cut Some Red Tape in Prescriptions. Stateline. The Pew Charitable Trusts. https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2017/03/27/states-cut-some-red-tape-in-prescriptions. March 27, 2017.

Current Oncology Utilization Management Strategies

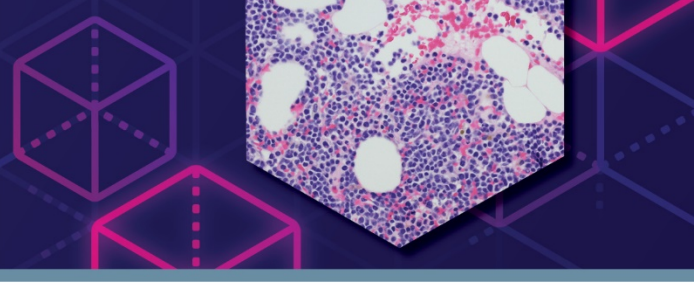


Due to growing number of available high cost oncology drugs, nearly all payers have implemented one or more of the following utilization management strategies:

Require a prior authorization/precertification based on indication.
Require evidence of disease progression before approving use of a non-preferred drug.
Restrict drug coverage to favorable molecular/biomarker test results.
Restrict molecular/biomarker test coverage based on evidence supporting their validity and cost-effectiveness .
Integrate oncology drug data across medical and pharmacy benefits to improve UM and clinical care management.
Integrate case management across medical and pharmacy benefits.
Offer a care management program for any cancer diagnosis.
Institute/increase peer-to-peer consultations with oncologists.

Adapted from: The 2016 Genentech Oncology Trend Report. 8th ed. https://www.gpbch.org/docs/2016_genentech_oncology_trend_report.pdf. South San Francisco, CA: Genentech; 2016. Accessed March 2017.

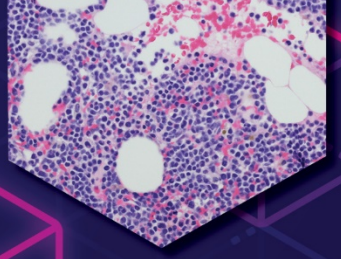
Balancing Benefit Design Factors and Member Cost-Sharing Considerations



- Member cost-sharing considerations
  - High cost share reduces access to care for many patients.
  - Adherence declines as cost rises, increasing overall healthcare costs.
  - Efficacy/tolerability of drugs associated with different price points
- Benefit design factors
  - Medical vs pharmacy
  - Copay vs Coinsurance/Deductibles
  - Specialty tiers
  - In-network vs Out-of-Network

Donahue, M. Future of Health Care Delivery and Benefits, Anthem BCBS. https://slideplayer.com/slide/5926878/. Accessed October 2018.

Current Environment of Copay Assistance



- While copay cards may improve patient access, affordability and adherence, some plan sponsors are concerned of unintended rise in total cost of care via:
  - Removing barriers to unnecessary testing/procedures by limiting patients' stake
  - Incentivizing patients to utilize non-preferred drugs
  - Minimize deductible benefit design ability to control use of other high cost services (e.g., ED vs urgent care or doctor's office visit; demanding greater number of higher cost imaging tests or genetic tests)

- Introduction of Accumulator Adjustment and Copay Allowance Maximization programs in 2017
  - Out-of-pocket dollars saved from copay assistance programs are not allowed to be applied toward member's deductible
  - Plan sponsors method to offset copay assistance programs' potential negative impact on management of total cost of care
  - However, when applied to high-cost/high-value drugs, these programs may create a barrier to patients' utilization of more complex therapies leading to actual increase in total cost of care.

Copay Assistance Mitigates Patient Cost Burden, but Accumulator Adjustment Programs Can Reintroduce Financial Barriers to Access

Finding the right sequence of therapies in a complex chronic disease such as cancer can be a challenge

- Treatment adherence can result in improved Quality of Life and decreased health care utilization

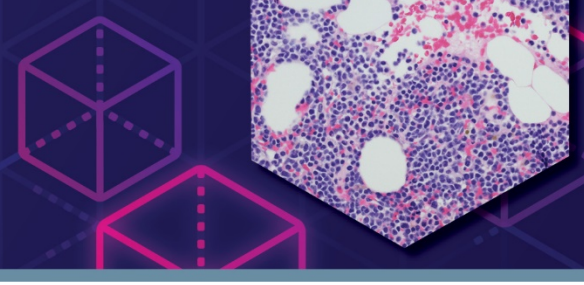
Patients with cancer often rely on copay assistance programs to mitigate the financial burden of cost-sharing

- Growing number of patients now only have high-deductible plan options
- Copay assistance programs are offered by manufacturers of specialty drug products for up to $x total out of pocket (OOP) offset
  - $0 copay card maximum OOP threshold reached within short timeframe
  - Patient will be in midst of treatment

Copay Accumulator Programs' unintended negative consequences:

- Accumulator adjustment and copay allowance maximization allows OOP deductible contribution to remain leading to no access to necessary drug therapy for some patients
  - ↑ **ER/Hospitalization use**
  - Development of resistance for certain tumor types
  - Disease progression

Medication Administration Location Drives Costs



Drug Management Strategies

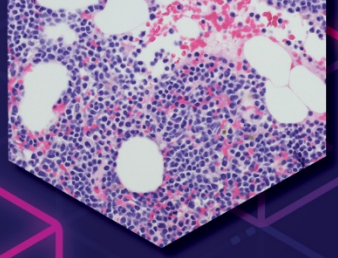
- Medical Claim Site-of-Care Optimization
- Pharmacy Channel Management

Site-of-care Example

Place of Service	Cost per Unit	Unit	Cost per Claim	Claims per Year	Annual Cost
MD office or home infusion	$70	50	$3,500	7	$24,500
Hospital Outpatient Facility (Medicare)	$111	50	$5,500	7	$38,850
Hospital Outpatient Facility (Commercial: percentage of charges)	$360	50	$18,000	7	$126,000

HOPD= hospital outpatient department
Internal Utilization and Pricing Data

Implementing Specialty Pharmacy Services



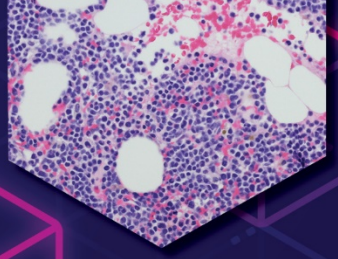
Program

- Specialty Pharmacy MTM
  - Guides benefit design
  - Improves utilization management
  - Integrates with care management through MTM
  - Ensures appropriate dosing
  - Promotes adherence and patient education
  - Includes drug dispensing component

Actions

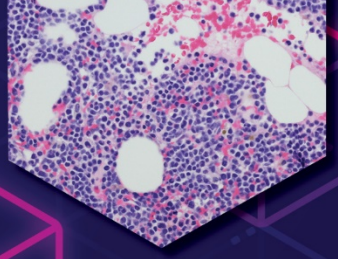
- Design program workflow and integration with care management
- Analyze utilization to select targeted drugs/disease states
- Train personnel:
  - Specialty diseases
  - Medications
  - Site-of-care logistics

Specialty Pharmacy Programs Help Control Cost and Improve Access



- Initial verification of benefits
  - Initial claim review—test claim (formulary, step therapy, and other payer requirements)
- Prior authorization and appeals
- Statement of Medical Necessity
- Patient financial concerns
- Copay programs
- Manufacturer Patient Assistance Program
- Alternative coverage organizations
  - Grants
  - Foundations

Care Coordination Improves Outcomes

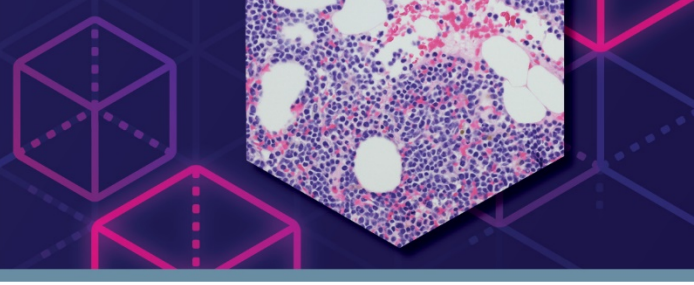


NCI Study

- Meta-analysis of 52 studies found care coordination improved 81% of outcomes, including screening, patient experience, quality end-of-life care.
- Most common care programs were:
  - Patient navigation
  - Home telehealth
  - Nurse case management

Gorin SS, Haggstrom D, Han PKJ, Fairfield KM, Krebs P, Clauser SB. *Ann Behav Med*. 2017;51(4):532-546.

Care Coordination Reduces Confusion and Costs

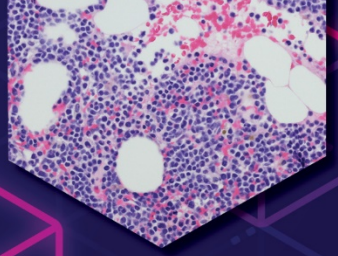


Meridian Health Systems:

- Care coordinator communicates with patient, family, multiple specialists.
- Reduces unnecessary imaging and testing.
- Reduces hospitalizations from manageable complications such as dehydration.
- Earns patient satisfaction scores higher than 90%.

Cryts A. Improve Care Coordination in Cancer Care: 2 Key Focus Areas. Managed Healthcare Executive. http://www.managedhealthcareexecutive.com/leukemia-and-lymphoma/improve-care-coordination-cancer-care-2-key-focus-areas. Published Mar 16, 2018. Accessed October 2018.

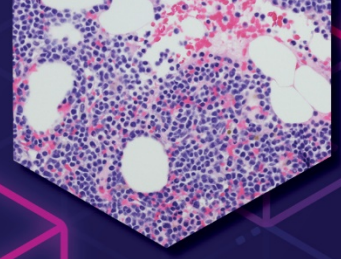
Health Coaches Reduce Costs, Increase Satisfaction



- Stanford
  - Health coaches discuss goals for life with advanced cancer patients facing treatment failure or with less than three-year anticipated survival at diagnosis. Estimated reduction in costs, mostly from end-of-life care, of 14.5%.
  - Health coach/nurse team assessed symptoms at intervention call center using decision-support systems. Prestocked, individualized medication bundles were made available. Decreased ED visits, hospitalizations. Estimated cost reduction of 14%.

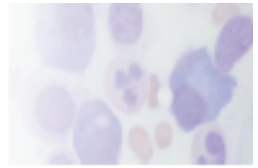
Patel MI, et al. Redesigning Advanced Cancer Care Delivery: Three Ways to Create Higher Value Cancer Care. *J Onc Pract*; 11(4):July1, 2015: 280-4.

Summary



- Oncology treatment costs continue to rise sharply, driven by multi-therapy regimens and targeted therapies.
- Utilization management more important than ever, but some traditional methods are now legislatively restricted and new ones may have unintended negative consequences.
- Balance needed between managing costs and maintaining patient access to treatment.
- Increasing patient share or restricting copay assistance in high deductible environment may lead to non-compliance and higher costs.
- Options include tie-in to EHRs to facilitate approvals, requiring pre-authorization only for non-pathway care, establishing site of care programs, using specialty pharmacy.
- Health coaching and care coordination control costs effectively reduce unnecessary tests and treatments and increase patient satisfaction and treatment alignment with patient goals.

Multiple Myeloma Clinical Primer



MULTIPLE MYELOMA CLINICAL PRIMER

Contents