ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Regional Lecture Series

Leveraging a Multidisciplinary Approach to Multiple Myeloma Care

ACCC
Association of Community Cancer Centers

Leveraging a Multidisciplinary Approach to Multiple Myeloma Care

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Learning Objectives

I. Discuss ways to tailor care plans based on goals, treatment, and patient preferences

II. Review ways to identify, assess, and manage patients with high-risk profile and biochemical relapse

III. Summarize guideline recommendations around prevention, diagnosis, and management of skeletal-related events

IV. Outline the role of the multidisciplinary team-based approach

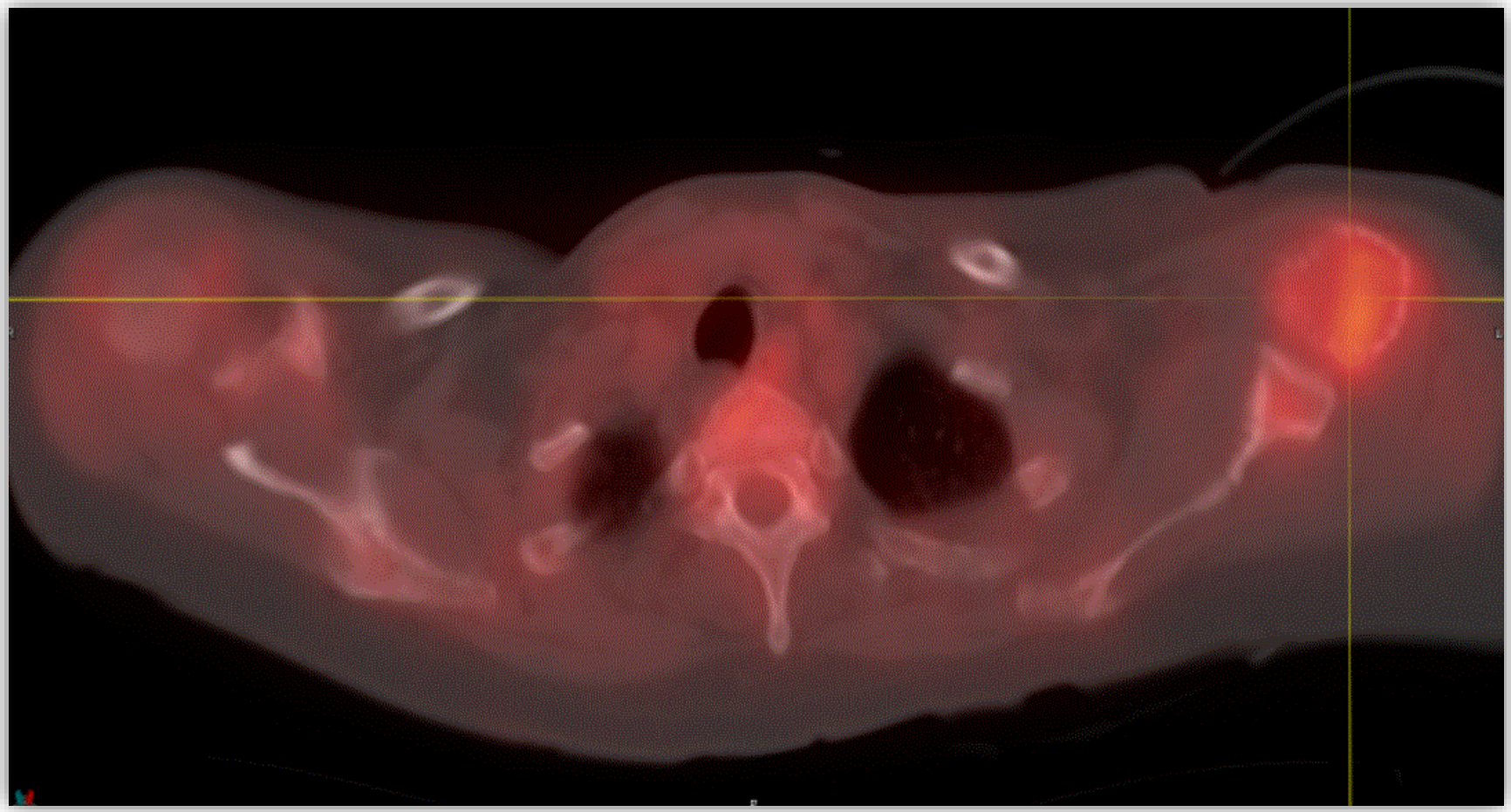
Multiple Myeloma Statistics

- In the United States, approximately 30,000 patients are diagnosed with multiple myeloma each year
- Compared to many cancers, multiple myeloma is relatively rare and represents approximately 2% of all new cancer cases in the U.S.
- In 2018, about 12,770 deaths are expected to occur (6,830 in men and 5,940 in women)
- 5-year relative survival for MM for cases diagnosed between 2007 – 2013 is 50%

Case

- 58-year-old woman was admitted to the hospital for left shoulder pain
- Patient was also found to have hypercalcemia (calcium of 18) and renal insufficiency (creatinine of 1.6)
- Patient treated with aggressive IV hydration and pamidronate
- Lytic lesion over left shoulder
- Pt. underwent left shoulder biopsy and bone marrow biopsy
- Hypercalcemia and renal insufficiency improved with initial treatment

Case



Case

Protein, Total g/dL	10.0 (H)
Albumin Electrophoresis g/dL	3.2 (L)
Alpha-1-Globulin g/dL	0.3
Alpha-2-Globulin g/dL	0.8
Beta Globulin g/dL	0.8
Gamma Globulin g/dL	5.0 (H)
Albumin/Globulin Ratio	0.46
M Component g/dL	4.8

Ig Kappa Free Light Chain mg/dL	0.8060
Ig Lambda Free Light Chain mg/dL	28.2 (H)
Kappa/Lamda FLC Ratio	0.0286 (L)
IgA mg/dL	33 (L)
Total IgG mg/dL	6290 (H)
IgM mg/dL	10 (L)
Beta-2 Microglobulin mcg/mL	3.78 (H)

Immunofixation showed Monoclonal IgG lambda

Case

- Bone marrow core biopsy showed marked plasmacytosis with 65% of the population composed of plasma cells
- FISH panel was POSITIVE for 1p-, 1q+, 4p-, 11q+, -13, 14q-, 16q-, +17 and 17p-. This is consistent with complex karyotype and high-risk disease
- ISS stage II
- High risk category by mSMART 2.0
- International myeloma working group risk stratification - grade 3/high risk category

Genetic Abnormalities in MM

- del(17p) and del(1p32), are considered high-risk abnormalities
- t(4;14), and 1q gains are considered intermediate-risk abnormalities

Published in: Aurore Perrot; Jill Corre; Hervé Avet-Loiseau; American Society of Clinical Oncology Educational Book 38, 675-680

Risk Stratification

Table 1. International Myeloma Working Group Risk Stratification[3]

	Grade 1 Low-Risk	Grade 2 Standard-Risk	Grade 3 High-Risk
Parameters	ISS I/II plus absence of *t(4;14)*, *Del17p*, or *+1q21* and age < 55 years	Others	ISS II/III plus *t(4;14)* or *Del17p*
Median OS	> 10 years	7 years	2 years
Percent of Patients	20%	60%	20%

Abbreviations: ISS, International Staging System; OS, overall survival.

Risk Stratification

Table 2. Revised International Staging System for Multiple Myeloma[4]

	Stage I	Stage II	Stage III
Parameters	ISS I plus low LDH plus absence of *t(4;14)*, *t(14;16)*, or *Del17p*	Not R-ISS I or III	ISS III plus high LDH or *t(4;14)* or *t(14;16)* or *Del17p*
5-Year OS	82%	62%	40%
5-Year PFS	55%	36%	24%
Percent of Patients	28%	62%	10%

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase; PFS, progression-free survival; OS, overall survival.

Case

- Revised international staging system (R-ISS) for multiple myeloma risk stratification places the patient in stage III category
- 40% 5-year overall survival; and
- 24% 5-year progression free survival

Case

- Transplant-eligible
- Treated with combination chemotherapy with lenalidomide, dexamethasone, and proteasome inhibitor
- Because of the high-risk features, patient was treated with carfilzomib. This is based on the recommendations by international myeloma working group committee - *Blood*. 2016 Jun 16; 127(24): 2955–2962
- Aspirin for venous thromboembolism prophylaxis (IMiDs)
- Acyclovir for herpes zoster prophylaxis with proteasome inhibitor

FORTE Trial

- Phase 3 trial comparing combination of carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (KRd) versus carfilzomib plus cyclophosphamide/dexamethasone (KCd)
- Patients assigned to KRd had superior outcomes –
  - stringent complete response/complete response (sCR/CR; 14% vs 4%)
  - near CR (32% vs 21%)
  - very good partial response (VGPR; 73% vs 57%; *P* <.001)
  - partial response (PR) (94% vs 86%)
  - rate of MRD negativity was 53% versus 29% (*P* = .002) in favor of KRd
- High-risk patients had similar outcomes to those found in the overall population

Frontline Therapy in Transplant Eligible

- Triplet regimens are better than doublets
- VRd (combination of lenalidomide, bortezomib, and dexamethasone) is the commonly used regimen in the United States
- KRd (carfilzomib, lenalidomide, and dexamethasone) is preferred in the high-risk population
- Studies utilizing 4-drug regimens are underway
- Upfront transplant is considered between 4 – 6 cycles of chemotherapy

Coordinating Care with Transplant Team

- Determine if patient is transplant eligible or not
- Early referral
- Plan for transplant between cycles 4 – 6 cycles
- Good communication between the teams
- Lenalidomide needs to be stopped 1 month prior to transplant
- Typically followed by transplant team for 1 – 3 months after transplant
- Vaccination scheduled after transplant

Case

- Radiation therapy to the shoulder for palliation – 2000 cGy in 10 fractions
- Requirement for pain medications subsided
- Patient was started on denosumab to prevent skeletal-related events
- Bone-modifying agents such as bisphosphonates or a RANK ligand (RANKL) inhibitor (e.g., denosumab) can be utilized for prevention or management of skeletal-related events
- On January 11, 2018, the FDA approved denosumab for the prevention of skeletal-related events among patients with multiple myeloma who have bone metastases

Oral chemotherapy adherence tracking program implementation at a medically underserved comprehensive community cancer center

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YUMA REGIONAL MEDICAL CENTER

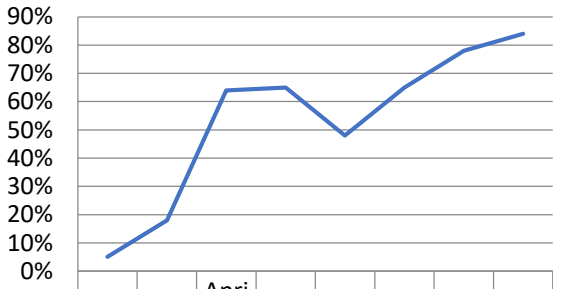
Background

- The field of oncology has witnessed a significant increase in the number of oral antineoplastic agents over the last several years and their utilization is expected to grow
- Several deficiencies in procedures for safe management and monitoring of oral chemotherapy regimens remain unaddressed
- There is paucity of data on impact of oral chemotherapy adherence to patient outcomes or emergency room visits

Methods

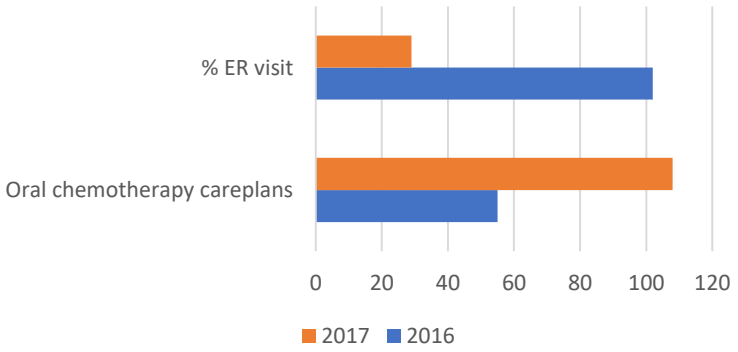
- Baseline oral chemotherapy adherence was tracked in new oral treatment plans
- This was supplemented with education of staff to run reports and increase chemotherapy tracking with special focus on education and follow ups
- Over 9 month period, the oral chemotherapy tracking process was implemented with the goal of 80% tracking being achieved
- Emergency room (ER) visits were calculated on patients having active oral chemotherapy care plans during a 3-month period before and after implementation of the program

Oral chemotherapy adherence rate



	Feb	Mar	April	May	June	July	Aug	Sept
Oral Adherence Tracking Completed	5%	18%	64%	65%	48%	65%	78%	84%

Graph showing reduction in ER visits



Results

- Reporting metric for compliance with oral tracking showed improvement from 5% completed reports to 84% completed reports over 9 months. The goal set to achieve 80% tracking was reached
- Prior to implementation of the program, over a 3-month period, 55 patients were receiving active oral chemotherapy care, with 56 encounters of ER visits by 30 patients related to their cancer. With consistent 80% chemotherapy tracking in place, we analyzed data for another 3 month period. During this 3-month period, 108 patients were receiving active oral chemotherapy, with 31 encounters of ER visits by 17 patients for their cancer

Conclusions

- Implementation of a tracking program for oral chemotherapy led to 72% reduction in emergency room visits by patients on oral chemotherapy care plans
- We were successfully able to implement an oral chemotherapy adherence tracking program in a medically underserved comprehensive community cancer program
- A prospective study can further validate the findings of this study

Minimal Residual Disease

- The next-generation sequencing (NGS) assay clonoSEQ has gained FDA approval as a test for minimal residual disease (MRD) in patients with multiple myeloma
- The assay detects as few as 1 tumor cell within more than 1 million healthy cells
- Need bone marrow biopsy
- Conventional multiparametric flow cytometry, which can detect 1 myeloma cell among 10,000 healthy cells
- 233 patients were detected as MRD-negative by flow cytometry, but assessment by clonoSEQ showed that 113 (48%) of those patients were MRD-positive

Minimal Residual Disease

- MRD-negative patients had increased PFS both before and after completion of maintenance therapy
- Patients who had sustained MRD negativity or who became MRD-negative at the end of maintenance had superior PFS (*P* <.001) and overall survival (*P* = .004)
- MRD-negative patients had overall survival of 94% compared with 79% for MRD-positive patients 4 years after the start of maintenance therapy

Perrot, Aurore, et al. "Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma." Blood (2018): blood-2018.

Transplant Ineligible Patients

- SWOG S0777 study compared RVd [lenalidomide, bortezomib, and dexamethasone] versus Rd [lenalidomide and dexamethasone] in newly diagnosed myeloma patients. 3 drug regimen was superior -
  - PFS (primary endpoint) was superior—43 months Vs 30 months. HR of 0.71
  - OS - benefit of 75 months versus 64 months. HR of 0.71
  - Response rate—82% versus 72%
- RVd-lite regimen (35-day regimen) - lenalidomide reduced to a dose of 15 mg for days 1 through 21. Bortezomib subcutaneously once weekly at a 1.3 mg/m^2 dose. Dexamethasone was given at a dose of 20 mg on the day of, and after bortezomib

Transplant Ineligible Patients

- ALCYONE trial - quadruplet regimen of daratumumab with VMP [bortezomib, melphalan, and prednisone] versus VMP
- Progression-free survival was 71.6% with the quadruplet regimen versus 50.2 months with the triplet regimen
- VMP is not used as first-line therapy in USA
- CyBorD [cyclophosphamide, bortezomib, and dexamethasone] is also acceptable option in this population – can be used in patients with renal insufficiency

Relapsed MM

- 3 drug combinations are preferred if patient is able to tolerate it
- Daratumumab – monoclonal antibody that targets CD38
- CASTOR trial – Vd-dara vs. Vd. ORR 82.9% vs. 63.2%, VGPR 59.2% vs. 29.1% and CR 19.2% vs. 9%
- POLLUX trial – Rd-dara vs. Rd. ORR 93% vs. 76%, VGPR 76% vs. 44%, CR 43% vs. 19%, MRD-negative 22.4% vs. 4.6%
- Elotuzumab is approved in combination with lenalidomide and dexamethasone

Case

- Treated with 4 cycles of KRd regimen and achieved VGPR
- Patient underwent autologous stem cell transplantation
- She received high-dose melphalan 200 mg/m^2
- Consolidation treatment with 2 cycles of KRd
- Maintenance therapy with ixazomib 4 mg oral days 1, 8, and 15 for a 28-day cycle along with lenalidomide 10 mg orally daily
- Denosumab will be continued for 2 years

Once-Weekly Dosing Option of Carfilzomib

- FDA has approved once-weekly dosing option of carfilzomib (Kyprolis) for use in combination with dexamethasone for patients with relapsed/refractory multiple myeloma
- Carfilzomib administered once weekly at 70 mg/m^2 with dexamethasone resulted in a prolonged progression-free survival (PFS) of 11.2 months (95% CI, 8.6-13.0) compared with 7.6 months (95% CI, 5.8-9.2) for the standard twice-weekly schedule of carfilzomib at 27 mg/m^2 with dexamethasone (HR, 0.69; 95% CI, 0.54-0.88; one-sided *P* = .0014). These data met the primary endpoint of PFS
- Overall response rate (ORR) in patients in the once-weekly arm was 62.9% (95% CI, 56.5-69.0) versus 40.8% (95% CI, 35.5-47.3) in the twice-weekly arm

Moreau, Philippe, et al. "Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (ARROW): interim analysis results of a randomised, phase 3 study." The Lancet Oncology (2018).

Role of Immunotherapy in MM

- **KEYNOTE-183**: A randomized, open-label phase 3 study of pembrolizumab in combination with pomalidomide and low-dose dexamethasone in refractory or relapsed and refractory multiple myeloma
- **KEYNOTE-185**: A randomized, open-label phase 3 study of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in newly diagnosed and treatment-naive multiple myeloma
- Increased severe adverse events
- No increased efficacy when combined with IMiD and dexamethasone

Chimeric Antigen Receptor (CAR) T-Cell Therapy

- Patients with relapsed or refractory multiple myeloma (MM) received bb2121, a second-generation CAR T-cell therapy targeting B-cell maturation antigen (BCMA)
- ORR of 95.5% with patients achieving MRD
- PFS of about 11.8 months
- 63% patients experienced cytokine release syndrome

Raje NS, Berdeja JG, Lin Y, et al. Abstract #8007. Presented at the 2018 ASCO Annual Meeting

ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Education Project

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Project Goals and Objectives

Greatly enhance the education of community providers and adoption of effective practices, including incorporation of the latest and best treatment options for patients diagnosed with multiple myeloma.

I. Raise awareness about education needs of healthcare providers in the community setting related to the management of multiple myeloma patients.

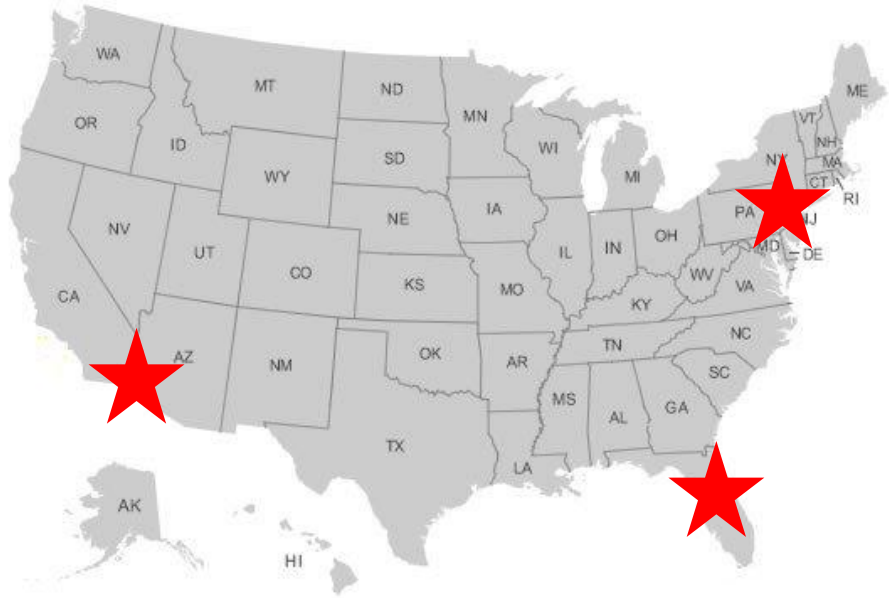
II. Educate the multidisciplinary healthcare team on how to implement effective practices in the treatment of multiple myeloma in community-based programs.

III. Establish vetted and designated resources for multiple myeloma that will be an enduring source of information for providers.

IV. Convene a strong network of advocacy and professional partners to increase peer-to-peer learning and adoption of effective practices.

Site Visits

- **Yuma Regional Medical Center Cancer Center**
  - Yuma, Arizona
  - *Comprehensive Community Cancer Program*
- **John Theurer Cancer Center at Hackensack University Medical Center**
  - Hackensack, New Jersey
  - *Academic Comprehensive Cancer Program*
- **Moffitt Cancer Center**
  - Tampa, Florida
  - *NCI-Designated Comprehensive Cancer Program*



International Myeloma Working Group (IMWG)

- Incorporating the latest guidance from the International Myeloma Working Group (IMWG) to improve diagnosis, assess prognosis, and develop tailored treatment plans

  - Diagnostic workup that includes flow cytometry, immunohistochemistry, cytogenetics, and molecular diagnostics
  - Revised International Staging System (R-ISS)
  - Assess risk profiles and engage in shared decision-making conversations with each patient
  - Refer patients who are eligible candidates for transplant evaluation

Skeletal-Related Events (SREs)

- Many patients with multiple myeloma have bony lesions and are often treated with either zoledronic acid (infusion) or denosumab (injection)
  - Monitor for side effects such as osteonecrosis of the jaw (ONJ)
  - Assess patient preferences
- Incorporating the 2018 ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Multiple Myeloma
  - Key clinical question: “What is the role of bone-modifying agents in patients with multiple myeloma?”
- Severe SREs such as spinal cord compression or vertebral compression fractures may occur
  - Often requires surgical management to prevent permanent paralysis

Advancing Research to Improve Care

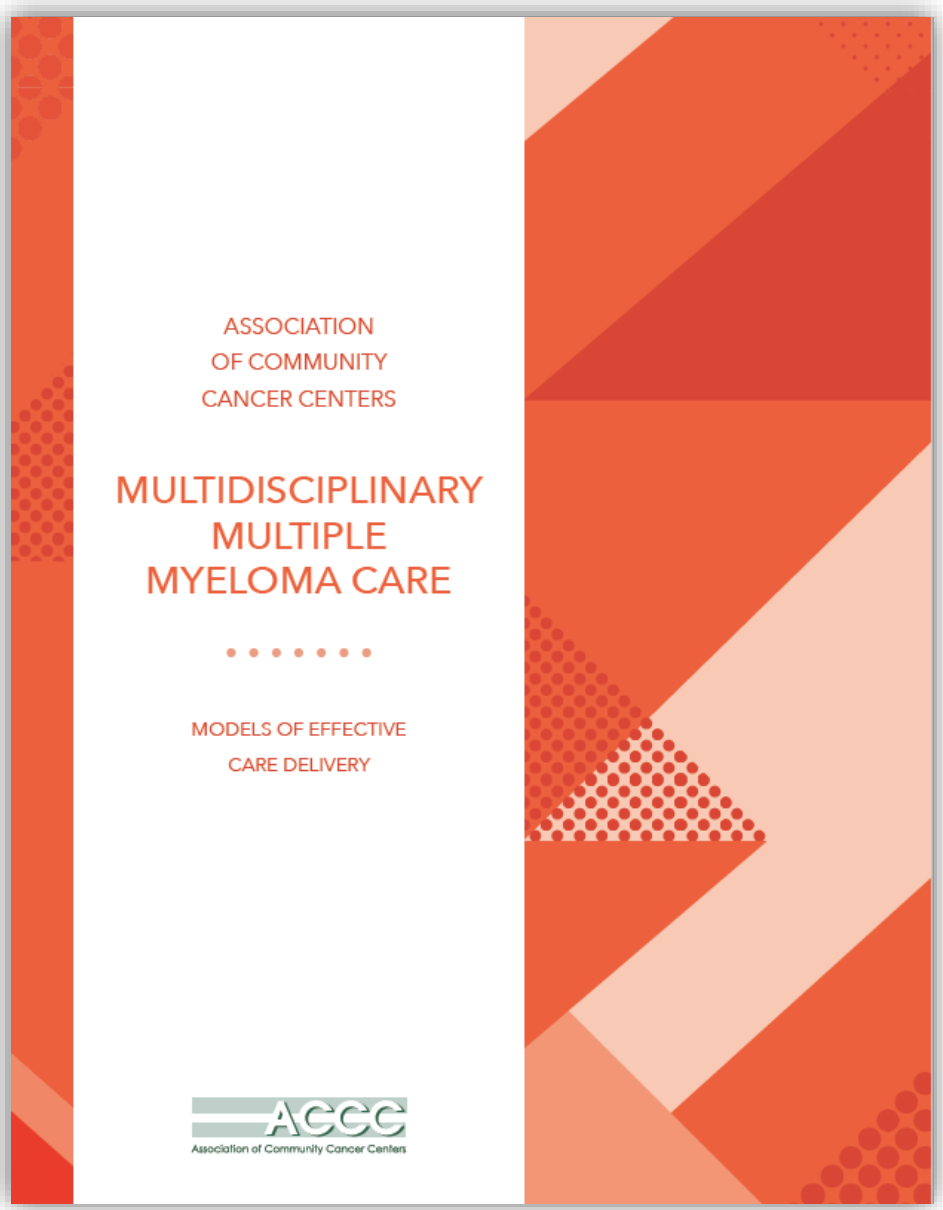
- John Theurer Cancer Center has been involved with the Multiple Myeloma Research Foundation (MMRF) CoMMpass (Relating Clinical Outcomes in MM to Personal Assessment of Genetic Profile) Study
  - Discovery of 12 different molecular types of multiple myeloma, each with its own level of risk

- Moffitt Cancer Center is a founding member of Oncology Research Information Exchange Network (ORIEN), a cross-institutional research partnership
  - Includes a longitudinal study called Total Cancer Care, which examines the effects of different cancers, treatment choices, and lifestyle so that physicians can have a better understanding of patient outcomes and treatment options

Project Webpage

- Advisory Committee
- Educational Resources
  - Regional lectures and recorded webinar
  - Resource Portal for HCPs
- Journal Supplement -
  - *October 2018 – *Print* Publication Now Available*

accc-cancer.org/multiple-myeloma-care



Models of Effective Care Delivery -

- Yuma Regional Medical Center Cancer Center
- John Theurer Cancer Center at Hackensack University Medical Center
- Moffitt Cancer Center

Questions?

Thank You!