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Research priorities in geriatric oncology for 2013 and beyond

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Abstract

The incidence of cancer increases with advanced age. Unfortunately, there is a significant lack of evidence regarding the safety and efficacy of treatments. The oncology community also lacks information regarding which older patients are most likely to benefit from treatment without undue toxicities. Interventions to lower symptoms and reduce long-term complications from cancer and cancer treatment in older patients are urgently needed. Establishing research priorities in geriatric oncology could help guide researchers and focus efforts on interventions that have the highest likelihood of improving outcomes. The Cancer and Aging Research Group, in partnership with the National Institute on Aging and National Cancer Institute, held linked conferences as part of a U13 grant in September of 2010 and November of 2012, summarising the gaps in knowledge in geriatric oncology and recommending ways to close these gaps. The overall purpose of this review is to highlight the important research priorities in geriatric oncology from the literature and from the previous U13 meetings. More evidence regarding the treatment of older cancer patients is urgently needed given the rapid aging of the population.

Approximately 60% of all cancers and 70% of cancer mortality occur in people aged 65 years and over.[1] It is anticipated that 70% of all cancer diagnoses will occur in adults aged ≥ 65 by the year 2030.[2] Because clinical trials include only a small proportion of older patients,[3] we lack important and necessary information on efficacy and safety of therapeutic oncology treatments in patients who are older, with health status issues besides their cancer.

Older cancer patients often have other health status concerns. For example, in a group of older patients with newly diagnosed cancer from a population-based database, 15% had three or more significant comorbidities, disability and geriatric syndromes (figure 1). The Comprehensive Geriatric Assessment (CGA) is an evaluation tool utilised by geriatricians to assess an older patient's health status. CGA includes an evaluation of functional status, comorbidity burden, cognition, social support system, nutrition and medication review. Studies of geriatric oncology patients reveal that measures within CGA can predict postoperative morbidity, toxicity of chemotherapy and mortality.[4] Because of the perceived importance of the CGA in the geriatric oncology community, research has focused on

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defining the reliability and predictive value of the CGA in cancer patients. Although the oncology community has come a long way in recognising aging issues, there is much more that could be done to improve the outcomes of older cancer patients. Below, we summarise research priorities in geriatric oncology for 2013 and beyond.

Incorporate geriatric assessment tools into clinical trials that predict adverse outcomes for older adults with cancer

Currently, oncologists assess functional status by assigning a Karnofsky performance status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status score,[5,6] generic scales which are a one-item numeric global assessment of functional status rated by the healthcare provider. They are applied to all adult cancer patients, regardless of age, and are used to estimate functional status in order to determine a treatment course, assess eligibility for clinical trials and predict treatment toxicity and survival.[7,8] Although KPS and ECOG performance measures are commonly used and do correlate with treatment toxicity, these tools do not predict survival or outcomes as well as CGA in the elderly.[9–11] For this reason, according to the National Cancer Comprehensive Network guidelines, CGA should be a key part of the treatment approach for older cancer patients.[12]

Key domains within the CGA are assessments of functional status and physical performance. Commonly utilised tools for evaluation of functional status in the geriatric population are evaluation of ADLs (Activities of Daily Living) and Instrumental (I)ADLs. ADLs are skills required for basic self-care,[13] and IADLs include the ability to perform daily tasks required for independent living.[14] The need for ADL and IADL assistance has been associated with poorer overall survival in geriatric oncology patients.[15] Older cancer patients have a higher prevalence of ADL and IADL deficiencies when compared to age-matched controls.[16] Physical performance measures objectively evaluate mobility and fall risk.[17,18] Objective measures of physical performance include the Short Physical Performance Battery, gait speed, six-minute walk test, chair stands, isometric grip strength and the ‘Timed Get Up and Go’ test. These directly observed measures can supplement self-report measures of functional status.

Other domains in the CGA, such as an assessment of comorbidity, nutritional status and cognition, can also identify older cancer patients at risk for adverse outcomes. Among cancer patients, comorbidity is associated with poorer treatment tolerance and overall survival.[19–23] Furthermore, patients with comorbid conditions often take several medications which may predispose patients to the risks of polypharmacy and drug-drug interactions.[24] Poor nutritional status is associated with an increased need for functional assistance and poorer overall survival in the geriatric population.[25] Unintentional weight loss during the six months prior to chemotherapy is associated with lower chemotherapy response rates and lower overall survival.[26] High-risk patients can be identified through self-reported weight loss of >10% of body weight, calculation of Body Mass Index (BMI) with BMI < 20 associated with adverse outcomes, and/or the Mini-Nutritional Assessment (MNA). The MNA has been shown to be a sensitive and specific tool for identifying malnutrition in the elderly population.[27] A cognitive assessment is needed to determine if the patient has the capacity to consent to treatment, to adhere to supportive care medication

instructions and to understand the indications to seek attention. In the presence of cognitive impairment, the involvement of the patient's family or caregiver is required to maintain safety.[28–31] In both the geriatric and oncology literature, social isolation has been linked to an increased risk of mortality.[32–34]

Two studies have rigorously evaluated the role of CGA for predicting toxicity from chemotherapy. In a study led by Hurria and performed by the Cancer and Ageing Research Group (CARG) (n = 500), CGA variables were associated with grade 3–5 toxicity.[35] A risk-stratification schema which scored patients from 0–23 was developed. Factors that were associated with risk included age ≥72, GI or GU cancer type, receiving full standard dose or more than one chemotherapy agent, the presence of anemia [<11G/dL (male), <10G/dL (female)] or renal insufficiency (creatinine clearance <34 ml/min) a recent fall, having hearing impairment, needing assistance with IADLs, limited in walking one block and having decreased social activity. A second study, led by Extermann, developed the Chemotherapy Risk Assessment Scale for High-Age Patients Score in over 500 patients.[36] The best model for hematologic toxicity included IADL score, LDH level, diastolic blood pressure and chemotherapy intensity. The best predictive model for non-hematologic toxicity included performance status, Mini-Mental State Examination score, MNA score and chemotherapy intensity. Information from two-thirds of the patients was used to develop the risk stratification scheme, and the tool was validated in the remaining one-third of patients.

CGA can also help predict overall survival. One study performed by Kanesvaran et al. evaluated the impact of CGA domains on overall survival and developed a prognostic scoring system, including these elements for use by clinicians. This study included 249 patients of any cancer type, stage and functional status. The majority of patients had GI, GU or lung malignancies, and 84.7% had advanced-stage disease. Factors that were independently associated with overall survival included low albumin, EGOG PS ≥ 2, abnormal geriatric depression screen, advanced stage disease, malnutrition and advanced age. A nomogram to predict one-year, two-year and three-year overall survival for individual patients, that weights each of these independent variables, was created for use by clinicians.[37] More recently, two studies evaluated the predictive value of geriatric assessment tools for survival. Giantin et al examined the value of the Multidimensional Prognostic Index (MPI) in predicting mortality in 160 patients with inoperable or metastatic solid tumour malignancy.[38] The MPI was used to stratify individuals into three grades of mortality risk. By six months and 12 months, 34.4% and 46.9% of patients had died, respectively. In multivariable models, the MPI was able to predict six-month and 12-month mortality. Van der Geest et al. examined factors that predict mortality in patients undergoing chemotherapy for colorectal cancer.[39] Patients aged 70 and over were enrolled (n=143), with the sample including those receiving adjuvant (38%) or palliative (62%) chemotherapy in a single comprehensive cancer centre in The Netherlands.[39] Nutritional status (measured by the MNA) and frailty (Groningen Frailty Indicator) predicted mortality, but only in patients treated with palliative intent.

This research has shown that pre-treatment CGA variables can help identify older adults at increased risk of chemotherapy toxicity and help predict survival. However, we still need validation studies of several of these models for use for specific cancers and treatments.

Incorporation of validated tools into clinical research, and potentially clinical care, can help identify which older patients are the most likely to tolerate and benefit from treatment. These tools can be utilised in future research to identify and test interventions to reduce chemotherapy toxicity and improve outcomes in vulnerable older populations.

Test the ability of a geriatric assessment model of care for improving outcomes of older cancer patients

There is a critical gap in knowledge regarding how to improve outcomes in older adults with cancer.[40–42] Despite the fact that the majority of cancer patients are in older age groups, most oncologists have received little specific training in the care of older patients.[43] As a result, common problems facing an aging population of cancer patients may go unrecognised and produce serious consequences.[40,44] Although CGA may help predict risk from chemotherapy toxicity and survival in older cancer patients, there is no evidence-based approach regarding the use of specific interventions to reduce risk from cancer treatment. CGA-driven interventions were identified as an important area of research by geriatric oncology experts during the first U13 conference, and examples of interventions used within the University of Rochester and University of Chicago Specialised Oncology Care and Research in the Elderly clinics to address vulnerabilities in selected geriatric domains are listed in table 1.[45]

In community dwelling older adults, interventions guided by CGA improve health outcomes – including prevention of disability, reduction in the risk of falls, reduction in unplanned hospitalisations and decreased nursing home admissions – providing evidence supporting the use of a multidimensional approach in older patients.[46–48] Several studies have shown that the implementation of CGA and CGA-driven interventions into the clinical care of older cancer patients is feasible.[49–52] The Comprehensive Geriatric Assessment in the decision-making process in elderly patients with cancer: ELCAPA study illustrated that providing CGA information and geriatric assessment-driven interventions to oncology teams can influence treatment decisions, although outcomes from these changes were not measured.[50] Another pilot study showed that CGA affected the oncology treatment plan.[53] Unfortunately, there are few published randomised studies evaluating outcomes from CGA and CGA-driven interventions in older cancer patients. In a study by McCorkle et al,[54] geriatric nurse practitioners conducted CGA with cancer patients, and this led to a survival advantage of 67% in the intervention group compared with 40% in the control group. In a study by Goodwin et al, breast cancer patients in the CGA-driven interventions group were significantly more likely to return to normal functioning than the controls.[55]

A conceptual model (figure 2) demonstrates how information from CGA can guide interventions and decision-making. CGA-driven interventions and/or changes in chemotherapy treatment decisions (eg. selection of regimen, dosing of chemotherapy, use of supportive care medications) could improve outcomes.

There is a great need for randomised studies to evaluate CGA and CGA-driven interventions for improving decisions for cancer treatment and for improving outcomes. At this stage, there is no consensus on how to best incorporate CGA-driven interventions into oncology

care. Two studies are ongoing which will utilise expert opinion to develop a consensus of geriatric assessment and geriatric assessment-driven interventions in oncology. The next necessary step would be to test whether these approaches improve outcomes in randomised studies.

Understand the impact of oncology therapeutics in the general population of older cancer patients

Because the average age of patients enrolled on cancer clinical trials is lower than the average age of patients with the disease, and since older patients enrolled in clinical trials are generally healthier than most patients seen in practice, it is difficult to apply the results of clinical trials to patients in the general population.[56–58] More data on the safety and efficacy of treatments in older patients are needed.

There are several possible reasons why older patients are under-represented in clinical trials. First, these trials often have stringent inclusion and exclusion criteria which would preclude their ability enrol, such as excluding patients with certain comorbidities, mild organ dysfunction, or a history of a past cancer, even though these issues are unlikely to affect outcomes. Second, the infrastructure - time or resources, required to safely enrol older patients in studies - is not usually built into the study protocols. Therefore, it is often very difficult for older patients to travel to a tertiary care centre frequently for repeated study visits and procedures. As a research community, different structures and novel approaches to data collection, such as telemedicine, should be considered to allow for the inclusion of an appropriate proportion of older patients. Third, the majority of older adults are treated in the community, not at academic medical centres. Therefore, enrolment in clinical trials should also be more widely available in community oncology practices, where the majority of older adults with cancer are treated. Community oncology practices need to be reimbursed for the extra time and resources required to enrol and retain older patients in trials. Fourth, there is often a concern for higher toxicity in older patients, which speaks to the need for trials specifically for older patients with safety parameters and endpoints of relevance. Because of difficulties with recruitment and enrolment of older adults, only 9% of patients enrolled in registration trials were 75 years or older in FDA-registration trials.[44] This contrasts with the fact that approximately 30% of cancer patients are in this age range.

The oncology community needs to focus on developing trials where the results can be generalised to the population with the disease. The gap may only be able to be closed if multidisciplinary teams work together to design elderly-specific trials to include patients who are older and/or have other health status issues. All trials, especially trials studying therapeutics for cancers that occur commonly in older populations, should have a specific target accrual for patients aged 65 and over. These studies would provide data that are necessary for clinicians to utilise in daily practice.

Identify and test interventions to improve symptoms and maintain quality of life of older cancer patients

In addition to including these measures as part of the baseline evaluation, longitudinal inclusion of a CGA would further our understanding of the impact of both the cancer and its treatment on geriatric outcomes such as functional status and cognition. One large population database of mostly cancer survivors showed that cancer survivors were more likely to be vulnerable, have a disability, or to have geriatric syndromes than people without a history of cancer.[59] This data suggests that cancer and/or cancer treatment could have long-term consequences on the quality of survivorship in an older patient. Endpoints should be included in clinical trials that evaluate impact of therapies on geriatric domains. This is especially important in curative intent trials, or trials for cancers with a long clinical history.

Another routine part of clinical trials is to evaluate the toxicity of the cancer therapy. Toxicity of chemotherapy is generally graded by the National Cancer Institute Common Terminology Criteria for Adverse Events.[60] Grade 3 (severe or medically significant), 4 (life-threatening) or 5 (treatment-related mortality) toxicities are typically captured and reported in clinical trials and are considered to be 'dose limiting.' Grade 2 toxicities, such as diarrhoea or neuropathy, could also significantly affect quality of life in older patients and may also be 'dose-limiting' particularly in the geriatric population. Therefore, grade 2 toxicities should be captured. Trials should also report consequences of toxicities such as health care utilisation and changes in care. Hospitalisations, rehabilitation and transitions to a higher level of care, such as assisted living or nursing home, are important outcomes to capture so that these risks can be discussed with the patient during treatment decision-making.

There are some under-studied, but important long-term symptoms of cancer and cancer treatment that can affect quality of life and should be studied. Sarcopenia is the progressive generalised loss of skeletal muscle mass, strength and function. Cachexia has no uniform definition, and is a complex metabolic syndrome associated with cancer that is characterised by weight loss >10%, reduced food intake (<1500 kcal/d) and systemic inflammation (CRP >10mg/L).[61] It is estimated that 50% of people older than 80 years have sarcopenia. Half of all cancer patients lose some body weight; one third lose > 5% body weight and up to 20% of all cancer deaths are directly linked to cachexia.[61] To date, no clinically applied regimen has been completely successful in reversing cancer-associated muscle or weight loss. Interventions for these issues including cachexia and sarcopenia are needed to improve the quality of survivorship for the older patient with cancer. The third conference of the CARG-NIH U13 Grant, 'Geriatric oncology research to improve clinical care,' will address this research need by bringing a multidisciplinary group of researchers together to develop a research agenda focusing on interventions for improving the quality of survivorship of older and/or frail adults with cancer.

Conclusions

New priorities in geriatric oncology research focusing on the needs of older cancer patients are necessary to meet the needs of a rapidly aging population. Older patients, caregivers and

health care providers would ultimately benefit from research that improves the evidence base for oncology care in older adults. Significant current gaps in knowledge ultimately lead to wide variation in patterns of care in the treatment of older adults with cancer, potentially increasing health care burdens and costs due to both over and under-treatment of older adults with cancer. Focusing efforts on geriatric oncology research would provide a better evidence base to inform decision-making, with the ultimate goal of improving the quality of care of older adults with cancer.

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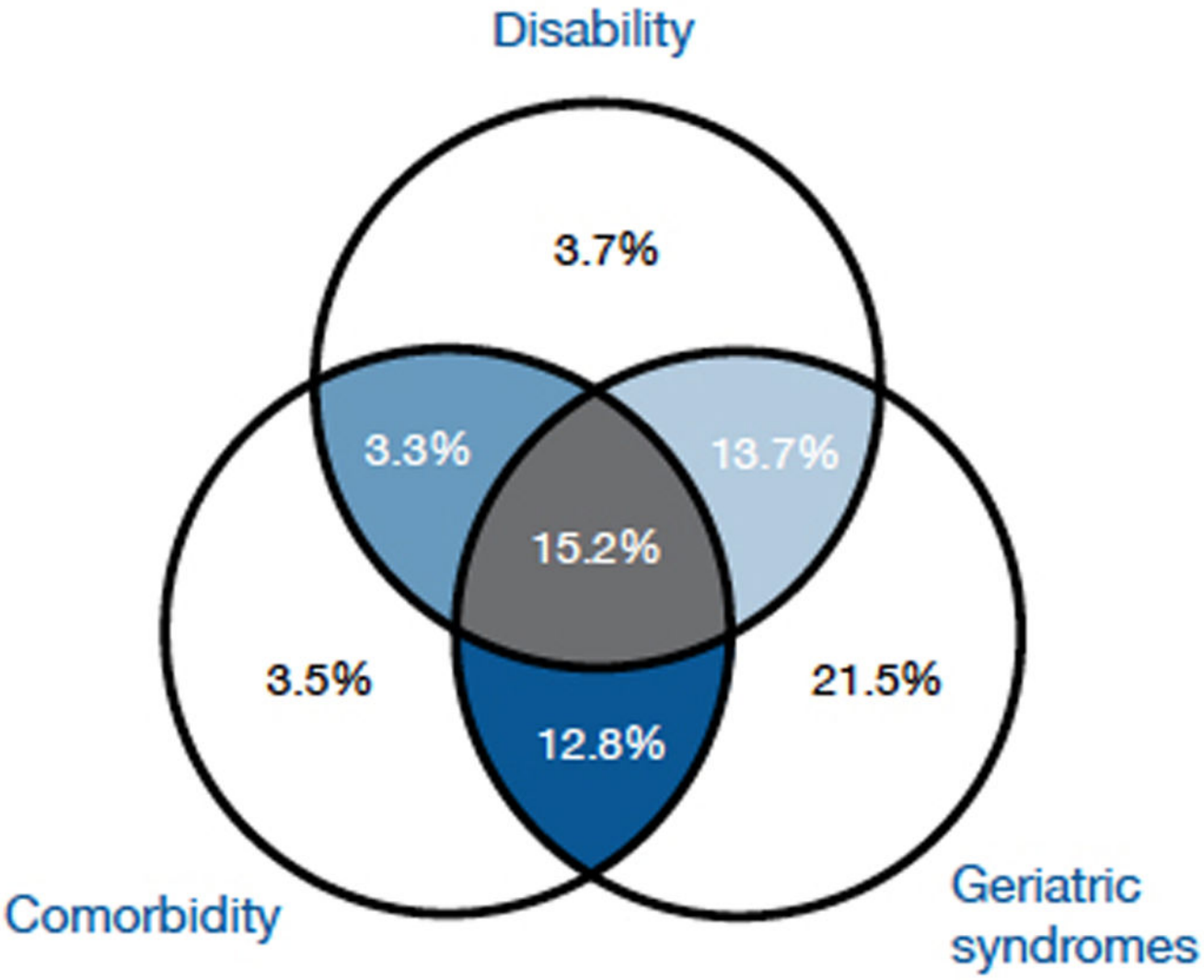

Figure 1.
Disability, comorbidity, and geriatric syndromes among older, newly-diagnosed cancer patients.

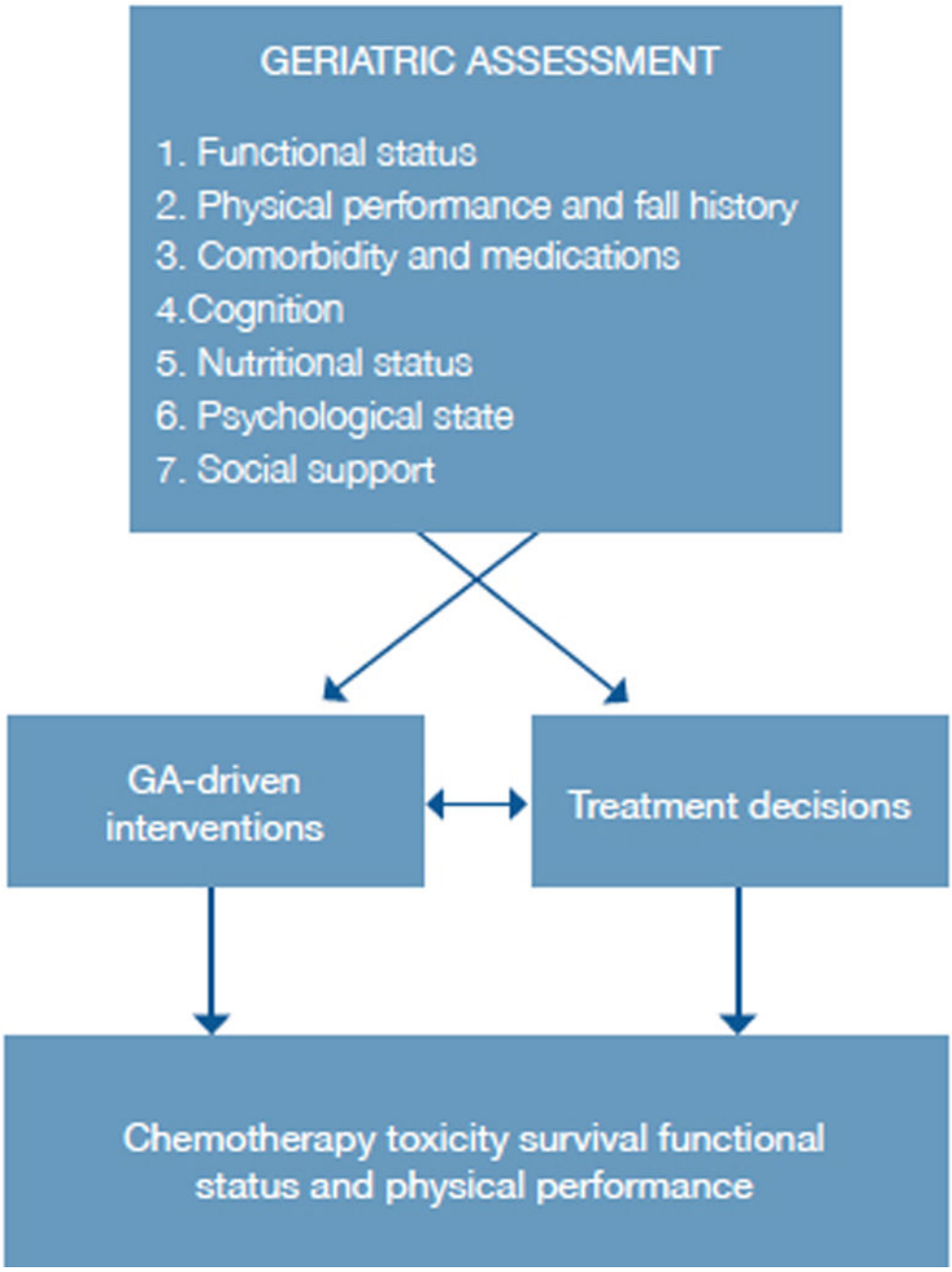

Figure 2.
Conceptual model of geriatric assessment use in chemotherapy choices.

Table 1

SOCARE Pilot Data on GA and GA-driven interventions

GA domains in relationship to cancer and chemotherapy in older adults	Examples of patient/ caregiver concern (from pilot work)	Rating of importance 0–10 with 10=very important median range		GA-driven interventions	Proportion
		Patient	caregiver		
Cancer treatment recommendations	- How does my (or my loved one's) age and underlying health status affect safety and efficiency of treatment? - will I (or my loved one) live longer with treatment?	7 (4–10)	8 (7–10)	- Change in type or schedule from original oncology recommendations - initial does reduction with escalation as tolerated - More frequent visits - change in supportive care medications	- 42% - 35% - 44% - 60%
Functional abilities, physical performance and/or falls	- How does my (my loved ons's) functional status affect tolerance ot chemotherapy? - How can l (or my loved one) maintain independence while on chemotherapy?	10 (8–10)	8 (6–10)	- Home/outpatient PT - Home/outpatient OT - Home safety evaluation - Personal emergency response system - Choose chemotherapy that is not neurotoxic if another option exists	- 30% - 19% - 12% - 30% - 30%
Comorbidity polypharmacy	- How do specific chronic diseases influence tolerance to cancer treatment? - How do we prevent side-effects from medications?	7 (0–10)	6 (0–10)	- Tailoring of medications - Elimination of dangerous medications - Referral to PCP or specialist for serious chronic medical condition	- 50% - 25% - 10%
Cognition	- How does my (or my loved ons's) baseline memory affect safety of chemotherapy? - What is the impact of chemotherapy on my (or my loved one's) memory?	9 (1–10)	8 (4–10)	- Assess decision-making capacity - Referral for further diagnostic work-up - Evaluation for reversible causes - Assess support and ability to take medication on own - Frequent visits to assess for delirium - Health care proxy - Social work	- 25% - 25% - 10% - 25% - 25% - 80% - 50%

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GA domains in relationship to cancer and chemotherapy in older adults	Examples of patient/ caregiver concern (from pilot work)	Rating of importance 0–10 with 10=very important median range		GA-driven interventions	Proportion
Psychological status	- My loved one is depressed and anxious. How can we help with this?	8 (0–10)	8 (4–10)	- Referral for counseling and social work - Antidepressant	- 25% - 25%
Nutrition	- What can we do to improve nutrition?	9 (6–10)	9 (6–10)	- Nutrition consult - Meals on wheels - Mouth and dental evaluation - Supplements	- 30% - 10% - 30% - 20%
Social support	- What are our resources for support at home to allow for safe delivery of chemotherapy?	8 (1–10)	7 (6–10)	- Aide services or higher level of care - Transportation assistance - Communtiy resources - Health care proxy and code discussion	- 20% - 15% - 40% - 75%