HOPA NEWS

Pharmacists Optimizing Cancer Care

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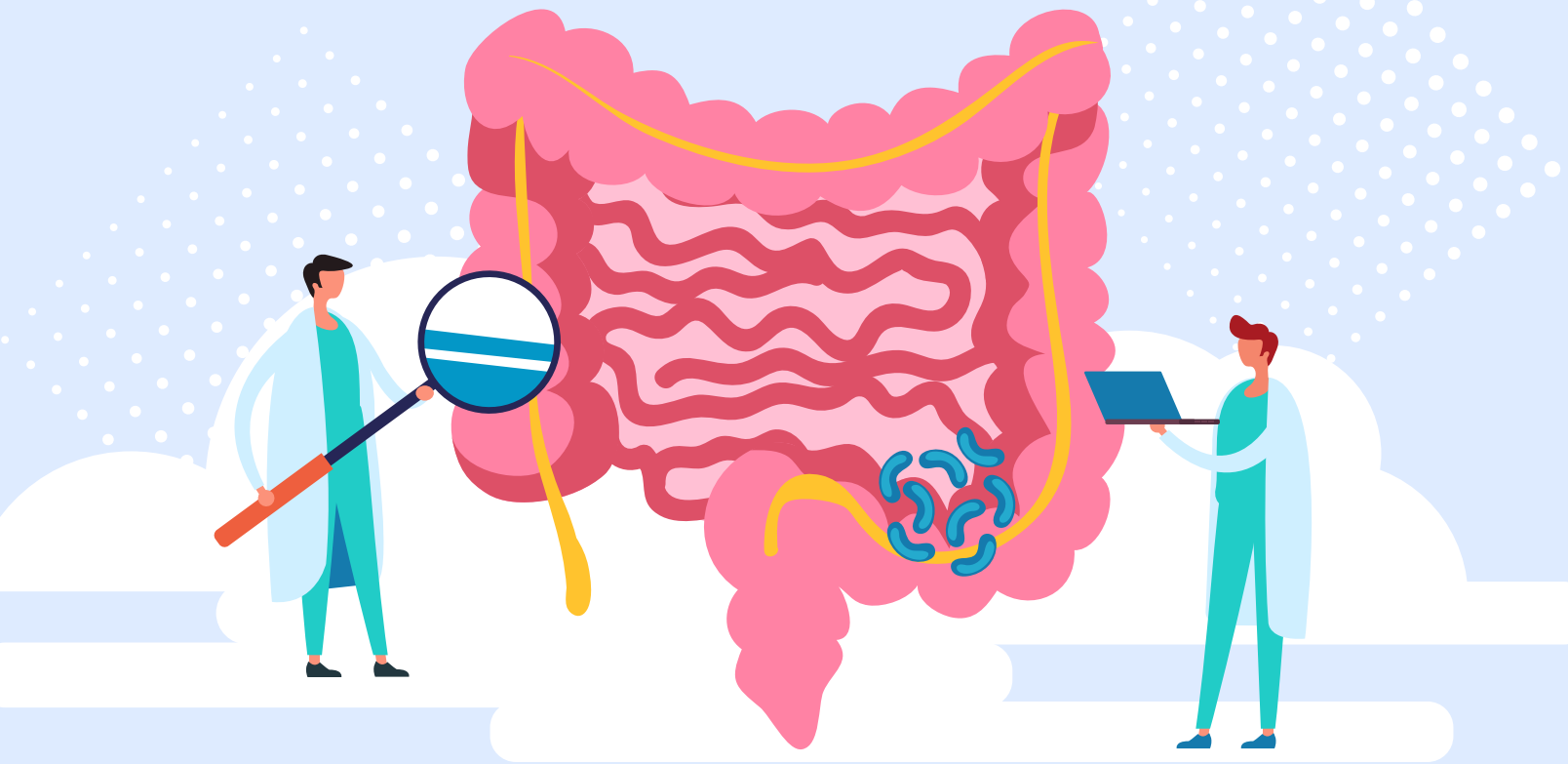

Beyond the Biopsy: ctDNA's Role in Colorectal Cancer Care

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Pharmacists Optimizing Cancer Care®

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Beyond the Biopsy: ctDNA's Role in Colorectal Cancer Care

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Cell-free DNA (cfDNA), also known as circulating tumor DNA (ctDNA), testing has emerged as a novel method that may be used in screening, monitoring, and therapy selection for certain types of cancer. cfDNA tests detect mutations in fragmented DNA in the blood to identify the presence of cancer cells or specific mutation status of genes, such as BRCA1/2 or EGFR. cfDNA refers to all double-stranded, non-encapsulated DNA fragments released by dying cells, while ctDNA refers to DNA specific to tumor cells, but the terms "cfDNA" and "ctDNA" are often used interchangeably in regard to testing in the oncologic setting. cfDNA testing is considered a type of "liquid biopsy", a blood- or body-fluid-based test to identify biomarkers of cancer cells.[1] There are several different methods currently employed for cfDNA testing.[1] PCR-based tests tend to have high sensitivity but can only be used for the detection of a few genetic alterations at a time. Next-generation sequencing and whole-genome sequencing tests allow for broader gene analysis, but at the expense of decreased sensitivity. Some tests may use methylation markers for identification of cancer cells. The utility of cfDNA testing varies depending on cancer type, as not all tumors shed enough cfDNA to be detected in the blood with current tests. Colorectal cancer (CRC) is known to shed a high amount of cfDNA, so cfDNA testing is rapidly being incorporated into CRC clinical practice.[2]

"...we can harness the power of ctDNA to improve early detection, monitoring, and treatment decision-making, ultimately leading to better outcomes for patients."

cfDNA Screening

Given the suboptimal rates of adherence to recommended CRC screening in the US, a less invasive testing method like a blood-based cfDNA test could have the potential to improve screening adherence. This may result in more individuals diagnosed in earlier, curable stages of CRC, if testing sensitivity and specificity is adequate. Epi proColon™ is a blood-based cfDNA screening test that detects methylation of the *SEPT9* gene for identification of CRC.[3] The test has been compared to both colonoscopy and fecal immunochemical testing (FIT). One trial included 1544 patients, with 44 patients found to have CRC via colonoscopy. CRC was identified with cfDNA-testing in 30 patients, for a sensitivity of 68%.[3] Another trial with 337 patients found a sensitivity of 73.3% for Epi proColon™ and 68% for FIT when compared to colonoscopy.[4] Epi proColon™ received FDA approval in 2016 but is only labeled for patients who have been offered and have a history of not completing USPSTF recommended screening.

The ECLIPSE trial was designed to assess the efficacy of a different cfDNA blood-based screening test called Shield™.[5] This test detects genomic changes and DNA fragment patterns in addition to methylation status for CRC identification. The trial included patients 45 to 84 years of age at average risk for colorectal cancer. A total of 22,877 patients were enrolled at centers across the US. Sixty-five of the patients were found to have CRC via colonoscopy, of which 74% were stage I, II, or III disease. Of those diagnosed with CRC, 83.1% also had a positive cfDNA test result. Although the sample size did not allow for formal correlation analysis, more advanced stages seemed to trend with higher sensitivity. Likewise, only 13.2% of the 1,116 patients with identified advanced precancerous lesions had a positive cfDNA test. Of the patients without any identified cancer or precancerous lesions, 10.4% had a false positive cfDNA test result. Based upon the ECLIPSE trial results, Shield™ was granted FDA approval in 2024, making it the first blood-based test approved for primary CRC screening. It has yet to be included in any CRC screening guidelines.

The sensitivity of 83.1% with Shield™ is similar to sensitivity rates with other available non-invasive screening methods like stool-based tests. However, it is notable that CRC was not identified in a significant number of patients. With the currently available cfDNA screening tools, tests like Shield™ and Epi proColon™ would ideally be used in conjunction with other validated screening methods like colonoscopy to minimize risk of false negative results. There is also potential for use in patients who decline or lack access to currently recommended screening methods. With improvements in specificity and further information about how often cfDNA-based screening should be performed, cfDNA testing could become a widely utilized screening test. However, it may be difficult to develop tests with very high sensitivity or specificity considering that tumor mutational profiles are unknown at the time of screening and tests must rely on detection of common mutations in CRC.[6]

ctDNA Disease Monitoring

With the utility of cfDNA used as screening in the general population, ctDNA has also gained traction as a biomarker for elevated risk of recurrence in early stage (I-III) resected colon cancer. Multiple studies have evaluated the correlation of ctDNA with disease relapse. One of the first major studies out of Denmark assessed serial blood samples for ctDNA in patients with resected stage I to

III colon cancer 14 days preoperatively, 30 days postoperatively, and then at every third month up through 36 months, patient death, or withdrawal from the study.[7] Of the 122 patients with baseline samples, ctDNA was detected in 108 samples (88.5%). The sensitivity was lowest for stage I disease at 40% and much higher for stage II and III disease at 92% and 90%, respectively. The postoperative day 30 samples were collected prior to adjuvant chemotherapy and available for 94 patients, of which only 10 patients were positive (10.6%). These patients had a much higher recurrence rate of 70% than the 11.9% of the ctDNA-negative patients. When the authors adjusted for confounders, the ctDNA positivity was the only significant prognostic factor for relapse. The authors were also able to get a glimpse into the effectiveness of adjuvant chemotherapy. Of eight ctDNA-positive patients who received adjuvant chemotherapy, four patients cleared ctDNA during treatment. Two of the four patients who cleared eventually regained ctDNA positivity (shortly after treatment). The six patients who either did not clear ctDNA at all or who regained cfDNA positivity all relapsed; the two patients who remained ctDNA negative had not relapsed at the time of publication. Similar studies in a broad population of early stage-colon cancer, and specifically stage III colon cancer, corroborated worse disease-free survival with ctDNA positivity post-surgery, as well as for those patients who remained positive throughout adjuvant chemotherapy.[8-10] One of the largest ongoing ctDNA studies, CIRCULATE-JAPAN, is following over 2,000 patients with ctDNA results available.[11] The GALAXY part of the study assessed prognosis: similar to previous studies, patients with ctDNA-positive disease have a significantly inferior disease-free survival compared to negative patients (HR 15.75; 95% CI, 12.59 to 19.68; $p < 0.0001$).

The DYNAMIC trial took these findings one step further and actually utilized ctDNA to guide adjuvant therapy decisions for patients with stage II colon cancer.[12] The benefit of adjuvant chemotherapy for patients with stage III resected colon cancer has been firmly established, however over 80% of patients with stage II disease can be cured with surgery alone. Current recommendations for adjuvant therapy in stage II disease rely on high-risk clinicopathological features, yet even in those patients the benefit is modest. The goal of the DYNAMIC trial was to create a more precise method for selecting patients that would truly benefit from adjuvant chemotherapy and avoid unnecessary exposure for those that may not benefit. Patients were randomized 2:1 to either ctDNA -guided management or standard of care based on risk factors. Treatment decisions in the ctDNA-guided group were made based on ctDNA samples taken at 4 and 7 weeks after resection. If either result was positive, those patients received adjuvant chemotherapy; patients with negative ctDNA received no chemotherapy.

A total of 455 patients were randomized; 294 in the ctDNA group and 147 patients in the standard group were included in the final analysis. The primary endpoint was noninferiority of ctDNA-guided management on recurrence-free survival at 2 years, which was confirmed. The proportion of patients surviving without disease recurrence at 2 years was similar between the ctDNA-guided group (93.5%) and the standard group (92.4%), however fewer patients in the ctDNA-group received chemotherapy (15% vs 28%). The relapse-free survival was sustained in the 5-year follow up presented at the 2024 ASCO Annual Meeting: 88% in the ctDNA-group vs 87% in the standard group.[13] The authors also presented overall survival, which was similar between the two study groups (93.8% vs 93.3%), but significantly worse for patients in the ctDNA-group with positive ctDNA who were treated vs ctDNA-negative patients who were not treated (HR 3.30; 95% CI, 1.02 to 9.05; $p = 0.014$).

In addition to using ctDNA in early-stage patients, patients with metastatic CRC may also benefit. Li and colleagues evaluated ctDNA in metastatic patients who achieved no evidence of disease (NED).[14] They enrolled 106 metastatic CRC patients with NED. About half the patients (51.9%) had positive ctDNA after curative treatment. These patients had significantly worse recurrence-free survival than those with negative ctDNA (HR 4.58; 95% CI, 2.18 to 9.64; $p < 0.001$), showing that ctDNA may be useful across the entire spectrum of CRC.

Despite the trending positive results of these trials, the NCCN® Panels for colon and rectal cancers caution against using ctDNA to estimate risk of recurrence or to determine aggressiveness of adjuvant therapy outside of a clinical trial at this time.[15,16] ESMO echoes this sentiment, with a report from the ESMO Precision Medicine Working Group recommending against using ctDNA to detect molecular residual disease and guide treatment decisions.[17]

With Epi proColon™ and Shield™ using cfDNA for disease screening, the incorporation of ctDNA for disease monitoring, and possibly as a tool to select out the most appropriate patients for adjuvant chemotherapy, might not be too far in the future. However, there are questions left open by these trials. When and how often should we test for ctDNA? How do we alter our treatment for consistently ctDNA-positive patients in the adjuvant setting knowing they are more likely to relapse? Do we eliminate chemotherapy if stage II patients are ctDNA-negative after surgery? As ctDNA technology continues to evolve, its potential to revolutionize CRC care becomes increasingly evident. By addressing the questions left unanswered by current trials, we can harness the power of ctDNA to improve early detection, monitoring, and treatment decision-making, ultimately leading to better outcomes for patients. ●●

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Translating Evidence to Patient Care: Reflections on Eight Years in Early Drug Development

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A colleague reminded me during a recent coffee catch-up that July 2024 marks my 8-year journey with the Early Drug Development service at Memorial Sloan Kettering Cancer Center. Over these years, I have had the privilege of being the inaugural clinical pharmacy specialist in this pioneering service, dedicated to conducting phase I/II trials of promising new cancer drugs for both adult and pediatric patients, encompassing various disease types and molecular targets. This period has coincided with the rise of precision medicine, basket trials, tumor-agnostic approvals, and groundbreaking immunotherapies, which have reshaped the landscape of cancer treatment.

When I first started in this role, a common question was how my responsibilities as a clinical pharmacist would integrate with multiple clinical departments and how I could collaborate with physician leaders. To address these challenges, I initially focused on foundational tasks such as reviewing study drug orders, screening for drug interactions, managing internal medicine issues, implementing national and institutional practice guidelines in daily practice, and educating patients on drug administration protocols. These responsibilities, rooted in my clinical pharmacy training, were crucial for ensuring patient safety and adherence to investigational protocols. Furthermore, these tasks facilitated the development of a strong rapport with physicians and research teams, fostering a collaborative environment where we could better understand each other's roles and strengths. This groundwork was vital in establishing a seamless integration within the service, ultimately contributing to the success of our clinical trials.

"The field of oncology is dynamic and demands agility, knowledge, and empathy."

However, driven by a passion for advancing patient care and guided by the evolving nature of early drug development, I soon expanded my responsibilities. A pivotal aspect became the management of side effects associated with novel therapies, grounded in a deep understanding of their mechanisms of action. Collaborating closely with multidisciplinary experts, we developed comprehensive toxicity management algorithms and published our findings, including the toxicity management of TRK inhibitors, ERK inhibitors, AKT/PI3K inhibitors, and RET inhibitors. This pharmacist-driven collaborative effort transformed evidence into patient care, contributing to enhanced drug delivery strategies and improving patient outcomes both locally and globally. These publications not only highlighted our work but also set new standards for toxicity management in early drug trials.[1-7]

A significant aspect of my journey involved participating in global collaborations, including the partnership between MSK and the Chinese Thoracic Oncology Group (CTONG), which advanced international clinical trials and regulatory harmonization. The MSK-CTONG collaboration connected us with international experts and research institutions, allowing us to share insights, harmonize protocols, and advance our collective understanding of complex cancer therapies. This global perspective enriched our approach to clinical trials and treatment strategies, enabling us to implement cutting-edge practices and drive innovation in oncology care. By collaborating with FDA on regulatory harmonization methods such as the Project Orbis, we were able to promote the simultaneous review of oncology products by regulatory authorities across more countries, thus potentially accelerating access to promising therapies for patients worldwide.[8] This alignment with international standards underscored our commitment to global collaboration in patient-centric clinical trials.

Despite sometimes being seen as a 'pan-tumor' specialist, implying a lack of focus on a single disease area, I welcomed the chance to learn across multiple therapeutic areas to drive practice change for different tumor types. This broad exposure helped me develop a diverse expertise, especially valuable in the fast-evolving field of oncology. I stayed committed to cutting-edge research and addressing unmet needs through innovative therapies targeting previously untreatable genetic alterations. My journey didn't stop at clinical practice. I delved into translational research and medicinal chemistry, working on early and preclinical studies to identify new drug candidates. I presented these findings to my team, bringing promising compounds into clinical trials at our institution. One significant area of my work involved targeting HER2 alterations from a pan-cancer perspective. I developed protocols for HER2-targeted therapies and presented the trial results, helping set new standards in this field. Collaborating with internal and external experts to conduct translational

Reflection on Personal Impact and Growth

research and generate real-world evidence in cancer treatment allowed me to continuously learn and deepen my understanding of novel therapies. My academic presentations and publications on real-world data also provided pharmaceutical companies with valuable insights for drug development. By translating evidence into patient care, I contributed to enhanced drug development strategies and improved patient outcomes.[9-11] Being able to move from identifying promising compounds to seeing them in clinical trials was incredibly rewarding and highlighted the seamless integration between research and clinical practice. This proactive approach has been crucial in bringing life-saving therapies to patients in need.

I further extended this experience as a preceptor for PGY-2 oncology pharmacy residency, which emphasized a broad approach rather than focusing on a single disease. This rotation highlighted the importance of understanding molecular biomarkers and utilizing tools like OncoKB and cBioPortal to explore cancer genomic data. We also focused on designing clinical trials to address unmet therapeutic needs. This comprehensive approach equipped me with the skills to navigate the complexities of modern oncology practice and fostered a new generation of clinical pharmacists adept at integrating molecular insights into patient care.

Reflecting on these eight years, I avoid categorizing myself as merely a 'specialist' in early drug development. The term 'specialist' suggests a finality that doesn't fit the ever-evolving nature of our work. Instead, I embrace continuous learning and personal growth. This journey has taught me the value of defining my own capabilities and consistently pushing my boundaries.

As I mark this milestone, my commitment to advancing cancer care remains unwavering. The field of oncology is dynamic and demands agility, knowledge, and empathy. My focus on translating evidence into actionable patient care has been central to my work, driving improvements in treatment strategies and patient outcomes. With more cancer centers developing services focused on early drug development in pan-cancer settings, I anticipate seeing more colleagues in roles like mine. I look to the future with optimism, eager to contribute to the next era of innovations that will bring hope and healing to patients worldwide. ●●

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A Day in the Life of an Oncology Pharmacist: Time-Saving Pearls for Every Role

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Introduction

Oncology pharmacists are notorious for working in a high-stakes, fast-paced setting with many responsibilities. Regardless of role, we often balance clinical duties, patient interactions, administrative tasks, teaching (both within our discipline and across disciplines), scholarly activity, and more. Frequently, these expectations can feel overwhelming without a strong time management strategy in place. Here, I hope to share some strategies to help oncology pharmacists navigate these daily responsibilities efficiently and effectively.

"Work-life integration should also encompass career-focused aspects like professional development and advancement, but with an emphasis on what truly excites you within your career."

Morning: Starting the Day with a Plan

We've all heard it – breakfast can be considered the most important meal of the day. Similarly, a well-organized morning routine could be one of the most important tasks of your day to support productivity and avoid decision paralysis. This morning routine should minimally include the following:

1. **Allocate time for daily task review and patient cases.** Set aside 5 to 10 minutes to review your workload for the day. What's the patient census today? What meetings do I have? What administrative tasks do I have?
2. **Prioritize these tasks effectively.** Spend an additional 5 to 10 minutes prioritizing these tasks. Doing so will ultimately be a very individualized approach, but a variety of methods exist to support you in how you'd like to prioritize (Figure 1).[1-3] The Eisenhower Matrix and ABCDE method are often used as mental exercises, but you can also take a more visual approach. If you prefer working with paper, consider drawing an Eisenhower Matrix or ABCDE grid and using sticky notes to represent individual tasks. This way, you can physically move the notes around as needed. For those who prefer electronic tools, a range of task management apps are available (my personal favorite is Todoist©), where you can assign priority levels corresponding to the sections of the Eisenhower Matrix or ABCDE grid.[4]

Figure 1.[1-3]

Eisenhower Matrix

A 4-category system that categorizes tasks as those that are (1) important and urgent, (2) important and not urgent, (3) not important but urgent, (4) not important and not urgent

	Urgent	Not Urgent
Important	**Do** these tasks *Examples include:* • *New chemotherapy order entry/review* • *Identifying a solution for patients scheduled to receive a drug tomorrow that is on shortage*	**Schedule** these tasks *Examples include:* • *Finishing minutes from this month's Oncology P&T* • *Working on an annual cost-savings initiative* • *Developing a presentation/lecture for next month*
Less Important	**Delegate** these tasks *Examples include:* • *Patient education session* • *Drug information questions* • *Follow-up phone calls/emails*	**Remove** these tasks *Examples include:* • *Unnecessary meetings* • *Spending time on emails not pertaining to you*

There may be situations when urgent and important tasks can also be delegated! Consider how you can use your fellow team members or learners that have a lower workload for the day.

ABCDE Method

A 5-category system that prioritizes based on the consequences of not doing a task.

A	Most important items; these tasks have significant consequences if not completed, such as not entering a chemotherapy order.
B	Tasks with some consequence, such as inconveniencing someone or not reviewing your emails in a timely manner.
C	Tasks with little to no consequences, such as reviewing the latest *New England Journal of Medicine* publications.
D	Tasks that can be delegated (which may overlap with A through C).
E	Tasks that can be eliminated.

All items in "A" should be completed before "B" and so on.

3. **Have a daily huddle or touchpoint with your immediate team members**. Have a team of 5 clinical specialists that work closely together? Or planning to have 7 infusion pharmacists staffing the chemotherapy satellite today? Consider a group chat message in the morning or at the start of the shift, where each person shares their top 3 priorities for the day. An example could be:

   Hi team! Top priorities today are: (1) chart review of patients on service – we have 15 patients admitted, 2 planned chemotherapy starts, (2) oncology P&T Meeting – will plan to spend 30min prepping prior to this meeting at 1pm, and (3) preparing the rotation calendar for the students that start rotation with me Monday.

   This helps the individual in narrowing down the focus for the day, while also helping the team understand the overall workload across the group. Another benefit to this approach is to identify individuals who have a lighter workload for the day. Encourage team members to identify themselves as "open for support" which can allow team members to offload some tasks for the day that can create a more balanced (and supportive) team structure.

Midday: Managing Clinical Workflows and Patient Care

Streamlining Medication Review and Order Verification

Whenever possible, use templates and auto-population tools in the electronic health record (EHR) to ensure consistency and save time. This is especially useful for documenting assessments and notes. Standardizing the language used in documentation for chemotherapy orders and interventions across your team can streamline processes and reduce the time spent deciding how to phrase recommendations.

Managing Patient Interactions Efficiently

While the duration of patient interactions can be unpredictable, you can employ strategies to stay on track, especially for scheduled visits or interactions. Whenever possible, spend 5-10 minutes preparing by defining your main goals for the visit. Use checklists and structured questions to guide the discussion and ensure you cover all necessary points. For visits that typically follow a standard format, such as initial oral chemotherapy education sessions, consider standardizing checklists across your team to ensure consistent messaging.

Maximizing EHR Efficiency

There is significant potential to enhance time efficiency by optimizing your use of EHR systems. Although each EHR system is different, it's beneficial to schedule a meeting with your IT department to explore how the EHR can support your daily workflow. Learn about available shortcuts to reduce clicks, utilize reports to quickly identify high-priority patients (e.g., those starting a new chemotherapy regimen), and discover data mining features that consolidate information you regularly review into a single dashboard.

While leveraging EHRs, it's also crucial to understand their limitations. For instance, if you collaborate with IT to create a dashboard displaying a patient's active medication list along with relevant lab values and vitals, be aware of how the dashboard handles missing lab results. Does it remain blank, prompting you to follow up later, or does it display the most recent available value, even if it's from several days ago? If the value is from several days ago, how obvious is it that the value is not from today? Understanding these limitations will help you remain vigilant about the information presented to you while still maintaining efficiency.

Afternoon: Navigating Interruptions and Workflow Disruptions

Handling Mid-Day Interruptions

The detrimental effects of interruptions and multitasking on the safe delivery of pharmacy services have long been recognized.[5,6] To mitigate these issues, establish designated "focus times" during your workday for uninterrupted work periods. Clearly signal these times both physically (e.g., with a sign or closed door) and virtually (e.g., by blocking off your calendar and muting non-urgent notifications). Additionally, evaluate your physical workspace to see if a designated quiet zone can be created for these focus periods.

Time-Blocking for Nonclinical Tasks

To improve your workflow, schedule dedicated times for administrative tasks that do not overlap with patient care. Clearly define the specific tasks to be completed during these blocks and set a firm end time for them. These administrative periods may or may not coincide with designated "focus times," so decide if you can accommodate interruptions for these tasks. Regardless, even outside of focus periods, consider muting notifications and setting specific times to check emails and handle non-urgent communications.

For managing your work intervals, you might try the Pomodoro Method, which involves working for 25 minutes followed by a 2 to 5-minute break.[7] This approach helps maintain alertness and engagement and provides insights into how much time is spent on each task, aiding in future self-reflection. Using a physical timer can help you stay on track with these intervals.

Maximizing the Value of Team Meetings

A key goal in time management is to minimize unnecessary meetings and ensure that necessary meetings are productive. Before scheduling or attending a meeting, consider if the discussion could be handled through asynchronous communication to achieve the same results. If a meeting is necessary, make sure to establish and distribute a clear agenda and objectives beforehand so that participants can prepare adequately. During the meeting, keep the conversation focused on actionable items. If unrelated topics come up, note them for discussion at a later time, either asynchronously or in a future meeting.

Late Afternoon: Wrapping Up and Preparing for the Next Day

Before ending your workday, allocate at least 15 minutes to review completed tasks, patient interventions, and any pending follow-up items. Develop a standardized handoff procedure for your team, whether it's for shift changes (e.g., daytime to evening) or between days (e.g., weekday to weekend, or weekday to weekday). Ensure

this handoff procedure includes a method for identifying high-priority patients who need immediate attention, especially if the EHR does not automatically highlight them.

After Work: Self-Care and Work-Life Balance

The Importance of Self-Care for Oncology Pharmacists:
In a national survey of 614 hematology/oncology pharmacists, the majority (62%) reported experiencing burnout. Pharmacists who reported high levels of burnout were four times more likely to consider leaving their current position (for reasons other than retirement) compared to those with lower burnout levels.[8] This burnout may also heighten the risk of serious chemotherapy medication errors, as even minor mistakes or oversights can have significant consequences.

Work-Life Integration Strategies
Often referred to as "work-life balance," a more accurate term might be "work-life integration" to emphasize the harmony between different areas of life, including career, self-care, and personal relationships.[3] Establish clear boundaries for disconnecting from work after hours—such as turning off notifications—and communicate these boundaries to your team. Set aside dedicated time for activities that support your health and wellness, whether it's spending quality time with family, exercising, or pursuing a hobby. Approach this routine with the mindset of recharging both emotionally and physically.

Work-life integration should also encompass career-focused aspects like professional development and advancement, but with an emphasis on what truly excites you within your career. How can you allocate time to prioritize these areas? These activities, whether paid or volunteer, should align with your personal passions and reconnect you with the "why" behind your decision to become an oncology pharmacist.

Wellness Toolkits
Several pharmacy organizations have developed wellness toolkits tailored to pharmacists at different stages of their careers.[9-11] These resources include a variety of offerings such as educational materials, podcasts, support groups, networking opportunities, and practical strategies that can be implemented by employers, employees, national associations, and boards of pharmacy.

Conclusion

In a fast-paced oncology pharmacy setting, effective time management is crucial for balancing clinical, administrative, and personal responsibilities. While structured routines and streamlined workflows are essential, it's equally important to personalize these strategies to suit your unique needs and circumstances. Building in flexibility allows you to adapt to unexpected challenges and maintain long-term success. Prioritizing team communication, EHR optimization, and work-life integration can reduce burnout and enhance both professional performance and personal well-being. By focusing on self-care, professional development, and a sustainable routine, pharmacists can maintain their passion and thrive in this demanding field. ●●

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Adult Solid Tumor Precision Medicine in Pharmacy Practice

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Precision Medicine Introduction

Precision medicine has revolutionized the treatment paradigms for patients with cancer. The advent of molecular diagnostics has led to the development of biomarker driven therapies in specific solid tumors, leading to individualized treatments for patients as opposed to the traditional "one size fits all" approach. Assessing for biomarkers is now considered a standard part of patient work up in several solid malignancies due to their ability to aid in diagnosis, prognosis, and therapeutic decision making.[1] The rapid evolution of these technologies requires healthcare professionals to be familiar with specific biomarkers for solid tumors, and the diagnostics tests associated with their detection.

"As precision medicine and the era of targeted therapies are advancing, pharmacist comprehension of the treatment landscapes of solid tumors and knowledge of testing modalities can improve patient outcomes."

Molecular Diagnostic Tests Used in the Evaluation of Adult Solid Tumors

Biomarkers can broadly be categorized into two different types: prognostic and predictive. Prognostic biomarkers provide information about patient outcomes and may aid in the selection of treatment, but do not predict response to treatment. Predictive biomarkers give information about therapeutic intervention for patients and can be used to dictate the appropriate use of targeted therapies.[2] Several molecular assays are used for the detection of these biomarkers, and are essential for the proper assessment of each patient who presents with a suspected malignancy.

Immunohistochemistry (IHC) is a staining technology that was originally introduced in the 1940s.[3] It uses antibodies binding to proteins to determine the level of protein expression in tumor samples. It is used to detect tumor specific antigens, protein products of oncogenes or tumor suppressors as well as proliferation markers and enzymes.[4] Examples of biomarkers that are detected via IHC include programmed cell death ligand 1 (PD-L1) and human epidermal growth factor 2 (HER2), with respective IHC assays being FDA approved for these biomarkers.[5] Identification of targets through IHC is convenient from an operational standpoint since it provides vital information about pathological protein expression in a tumor sample within days.[6] Limitations of IHC include lack of reproducibility, variations in institutional protocol staining techniques, and subjective interpretations by pathologists.[7]

In situ hybridization (ISH) is a cytogenetic technique that was developed in the 1980s. This procedure uses fluorescence (FISH) to assess the presence of chromosomal aberrations, including rearrangements, insertions, inversions, losses (deletions), and gains (amplifications). An example of a biomarker that is detected using FISH is HER2, where labeled complementary DNA strands for HER2 are compared to chromosome enumeration probe 17 (CEP17). HER2 is considered amplified if the HER2/CEP17 ratio is ≥ 2 with at least 4 copies of HER2 in each cell. FISH is advantageous to use due to its ease of manipulation and possible automation of scoring but is limited in that it may be time consuming and costly. [7,8]

Polymerase chain reaction (PCR) is a molecular procedure that was developed in the 1980s. It can synthesize and amplify DNA or RNA into billions of copies in only a few hours. Several types of PCR are used in the clinical setting such as quantitative PCR (qPCR or real time PCR) and reverse transcriptase PCR which are more sensitive than qualitative assays. Classically, PCR has been utilized to detect single gene alterations, such as mutations in KRAS in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).[4,7] Advantages of PCR include its simple manipulation, rapid turnaround time, and high sensitivity. Conversely, it requires specific instrumentation and experienced operators in a laboratory setting which may not be available at every institution.[7]

Next generation sequencing (NGS) has drastically transformed molecular diagnostics in oncology. Also known as massive parallel sequencing, it is a high-throughput technique that detects multiple genomic alterations including nucleotide substitutions, insertions, deletions, amplifications, and chromosomal rearrangements across the genome from a tumor sample.[6,7] Several assays are available for clinical use, with each having differences in library preparation/number of genes assessed, methods of sequencing and bioinformatics for data analysis.[9,10] Furthermore, both DNA and RNA NGS platforms are available, with RNA being more sensitive for fusions/rearrangements.[4] Furthermore, liquid based NGS platforms have been developed to use circulating tumor DNA (ctDNA) from patient blood samples and is minimally invasive while accounting for tumor heterogeneity.[11] NGS is advantageous since it can generate a large volume of information about a patient's disease at a relatively low cost with a turnaround time of weeks.[7,12] Limitations include

heterogeneity amongst assays, the inability for some assays to distinguish between cancer associated mutations and normal tissue, and lack of universal education among healthcare providers to interpret results.[13,14] Of note, older forms of sequencing, such as Sanger sequencing, are utilized at some institutions with the limitation of not assessing for multigene variants on one platform.[4]

Table 1. Select Adults Solid Tumor Biomarkers and NCCN Testing Recommendations

Biomarker	NCCN Recommend Assay	Solid Tumor Specific NCCN Recommended Testing[15]	Solid Tumor with FDA Approved Targeted Therapy[16]
ALK	NGS, FISH, IHC, and RT-PCR[17]	Ampullary, Mesothelioma, NSCLC, Thyroid, Pancreatic and Uterine	NSCLC
BRAFV600E	RT-PCR, NGS, and Sanger sequencing [17]	Ampullary, BTC, Colon, Esophageal, GIST, Glioma, H&N, Melanoma, Neuroendocrine, NSCLC, Ovarian, Pancreatic, Rectal, Thyroid, and Vulvar	Tumor Agnostic
BRCA1/ BRCA2	Germline sequencing, and NGS (somatic mutations)[18]	Ampullary, BTC, Breast, Ovarian, Mesothelioma, Pancreatic, Prostate, and Uterine	Breast, Ovarian, Pancreatic, and Prostate
EGFR	NGS, PCR, and Sanger sequencing[17]	Bone and NSCLC	NSCLC
ERBB2 / HER2	IHC, NGS, FISH, Sanger sequencing, and RT-PCR[17]	Ampullary, BTC, Bladder, Breast, Cervical, Colon, Esophageal, Gastric, H&N, NSCLC, Ovarian, Pancreatic, Rectal, Uterine, and Vaginal	Tumor Agnostic (only for protein overexpression)
ER/PR	IHC[18]	Breast and Uterine	Breast
ESR1	NGS, IHC, and RT-PCR[18]	Breast	Breast
FGFR2/3	NGS, FISH, RT-PCR, and IHC[19]	Ampullary, Bladder, BTC, GIST, Pancreatic, and Uterine	Bladder and BTC
FRα	IHC[20]	Ovarian	Ovarian
HRD/HRR	NGS[20]	Ovarian and Prostate	Ovarian and Prostate
IDH1/2	NGS, RT-PCR, and FISH[19]	Bone, BTC and Glioma	BTC and Glioma
KIT	IHC, PCR, and NGS[21]	GIST, Melanoma, and Vulvar	GIST
KRAS* (wild type), *KRASG12C	NGS, RT-PCR, FISH, and Sanger sequencing[17]	Ampullary, BTC, Colon, NSCLC, Rectal, and Pancreatic	Colon, NSCLC, and Rectal
***MET* exon 14**	NGS and FISH[17]	NSCLC	NSCLC
MSI-H/dMMR	IHC, NGS, and PCR[19]	Ampullary, Bone, Breast, BTC, Cervical, Colon, Esophageal, Gastric, H&N, Hepatocellular, Neuroendocrine, Ovarian, Pancreatic, Penile, Prostate, Rectal, Testicular, Thyroid, Uterine, and Vaginal	Tumor agnostic
NTRK1/2/3	NGS, FISH, IHC, and PCR[17]	Ampullary, BTC, Cervical, Colon, Esophageal, Gastric, GIST, Glioma, H&N, Hepatocellular, Melanoma, Neuroendocrine, NSCLC, Ovarian, Pancreatic, Rectal,Thyroid, Uterine, Vaginal and Vulvar	Tumor agnostic
PD-L1	IHC[17]	Bladder, Breast, Cervical, Esophageal, Gastric, H&N, Melanoma, Mesothelioma, NSCLC, Vaginal, and Vulvar	Bladder, Breast, Cervical, Esophageal, Gastric, H&N, NSCLC, Vaginal, and Vulvar
PIK3CA	NGS, FISH, and RT-PCR[18]	Breast and H&N	Breast
***PDGFRA* exon18**	IHC, NGS, and RT-PCR[21]	GIST	GIST
RET	FISH, RT-PCR, and NGS[17]	Ampullary, BTC, Breast, Cervical, Colon, Esophageal, Gastric, H&N, Hepatocellular, Neuroendocrine, NSCLC, Ovarian, Pancreatic, Rectal, Thyroid, and Vaginal	Tumor Agnostic
ROS1	NGS, FISH, IHC, and RT-PCR[17]	Ampullary, BTC, Esophageal, GIST, Melanoma, NSCLC, and Pancreatic	NSCLC
TMB-H	NGS[18]	Ampullary, Bone, Breast, BTC, Colon, Esophageal, Gastric, H&N, Neuroendocrine, Ovarian, Pancreatic, Penile, Prostate, Thyroid, Uterine, Vaginal and Vulvar	Tumor agnostic

ALK = Anaplastic Lymphoma Kinase; *BRAF* = V-Raf Murine Sarcoma Viral Oncogene Homolog B; *BRCA1/2* = Breast Cancer Gene 1/2; BTC = Biliary Tract Cancers; *EGFR* = Epidermal Growth Factor Receptor; ERBB2 = Erb-B2 Receptor Tyrosine Kinase 2; ER/PR = Estrogen Receptor/ Progesterone Receptor; *ESR1* = Estrogen Receptor 1; FGFR2/3 = Fibroblast Growth Factor Receptor 2/ 3; *FR*α = Folate Receptor alpha; H&N = Head and Neck Cancers; HRD = Homologous Recombination Deficiency; HRR = Homologous Recombination Repair; *IDH1/2* = Isocitrate Dehydrogenase 1/2; *KIT* = Proto-oncogene c-KIT; *KRAS wild-type/KRASG12C* = Kristin Rat Sarcoma Protein proto-oncogene; *MET* exon 14= Mesenchymal-Epithelial Transition exon 14; MSI-H/dMMR = Microsatellite Instability-High/Mismatch Repair Deficient; NSCLC = Non-Small Cell Lung Cancer; *NTRK1/2/3* = Neurotrophic Tyrosine Receptor Kinase; PD-L1 = Programmed Death Ligand 1; PDGFRA exon 18 = Platelet-Derived Growth Factor Receptor Alpha exon 18; RET = Rearranged During Transfection; RT PCR = Real-time Polymerase Chain Reaction; ROS1 = ROS proto-oncogene 1; TMB-H = Tumor Mutational Burden-High

Current Guideline Recommendations for Genomic Testing in Adult Solid Tumors

There are numerous gene alterations that have been identified that impact therapy selection in many solid tumor malignancies. Appropriate testing allows for the identification of potentially efficacious targeted therapies, as well as avoiding therapies that may be unlikely to provide clinical benefit. While it is outside the scope of this article, it is important for optimal use and interpretation of molecular results to understand the methodology, the limitations that exist in a specific methodology, and the spectrum of genomic alterations that are tested by the assay in use. The below table provides a summary of the testing recommendations by the National Comprehensive Cancer Network (NCCN) for specific biomarkers to be assessed in different solid tumors (Table 1). Not all biomarkers in the NCCN guidelines have FDA approved indications currently, but information in Table 1 is listed for cancers that potentially have options for FDA approved targeted therapies as of October 2024. For information on when to test for specific biomarkers, please refer to the individual NCCN guideline recommendations.

Pharmacist-driven strategies to overcome barriers to biomarker testing

Despite the importance of biomarker testing for patients with a variety of solid tumors, the uptake of testing in clinical practice has been variable[22]. One of the key contributors to this slow uptake is related to barriers in implementing testing for patients. While other obstacles exist, many of these implementation barriers can be addressed by pharmacists and other members of the health care team.

Implementation Barriers

As seen in Table 1, there are an ever-growing number of mutations and subsequent targeted therapies that oncologists can use to treat patients with solid tumors, with some having tumor agnostic indications. Pathologist driven reflex testing can reduce the time to identification of targetable mutations compared to waiting for an order from an oncologist.[22,23] While initial tissue samples from biopsies may be sufficient to diagnose cancer, there may not be enough to complete biomarker testing. Repeat biopsies for patients are costly and carry risks to the patient. Working with interventional radiology or the surgical team to ensure adequate tissue is obtained at initial diagnosis can be helpful in improving access to testing.[22] The need for additional tissue samples can further be reduced by implementing efficient molecular testing with a single broad panel, such as NGS, instead of multiple unnecessary single gene tests. A single broad panel may also reduce cost compared to multiple repeated single gene tests, ultimately improving testing rates.[22,24] It is worth noting that even though the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination (NDC) for initial and further NGS testing for all solid tumors with a companion diagnostic claim, NGS coverage outside of Medicare and Medicaid is still variable.[22,25,26]

Pharmacist Opportunities

When thinking about how pharmacists can help remove barriers to testing, this can be done before and after prescribing occurs. Given how fast the targeted therapy landscape is developing, pharmacists play a big role in providing education to not only patients on options for testing, but also educating the care team on new FDA approved precision medicine therapeutics. As targeted therapies are increasingly gaining tumor agnostic indications, it is important for pharmacists to be aware of optimizing treatment based upon pharmacogenomics. Since more targeted therapies are being evaluated in basket-style clinical trials, understanding what biomarkers have either an associated FDA approved targeted therapy or an available clinical trial is crucial. This perspective is invaluable at molecular tumor boards or multidisciplinary tumor boards to ensure all treatment options are represented.[27,28,29] After a targeted therapy has been prescribed, implementing pharmacy driven support for insurance approvals, evaluation and application of appropriate patient assistance programs, and navigating the specialty pharmacy ecosystem can assist patients with obtaining the prescribed medication.[29] Integration of genomic data into the electronic medical record (EMR) is being explored, and can optimize personalized medicine initiatives to ensure patients receive the best care.[30] Alerts can be used as a mechanism to ensure drug orders are reviewed in correspondence with appropriate genomic findings, which can lead to pharmacy interventions.

As precision medicine and the era of targeted therapies are advancing, pharmacist comprehension of the treatment landscapes of solid tumors and knowledge of testing modalities can improve patient outcomes. The information provided in this article is geared towards supporting pharmacist interventions through understanding the molecular assays used for biomarker detection in solid tumors, along with their associated targeted therapeutic options. With this information, pharmacists can potentially identify gaps in their practice to optimize patient care. ●●

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A Strategic Plan Update from HOPA's Executive Director

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HOPA Executive Director

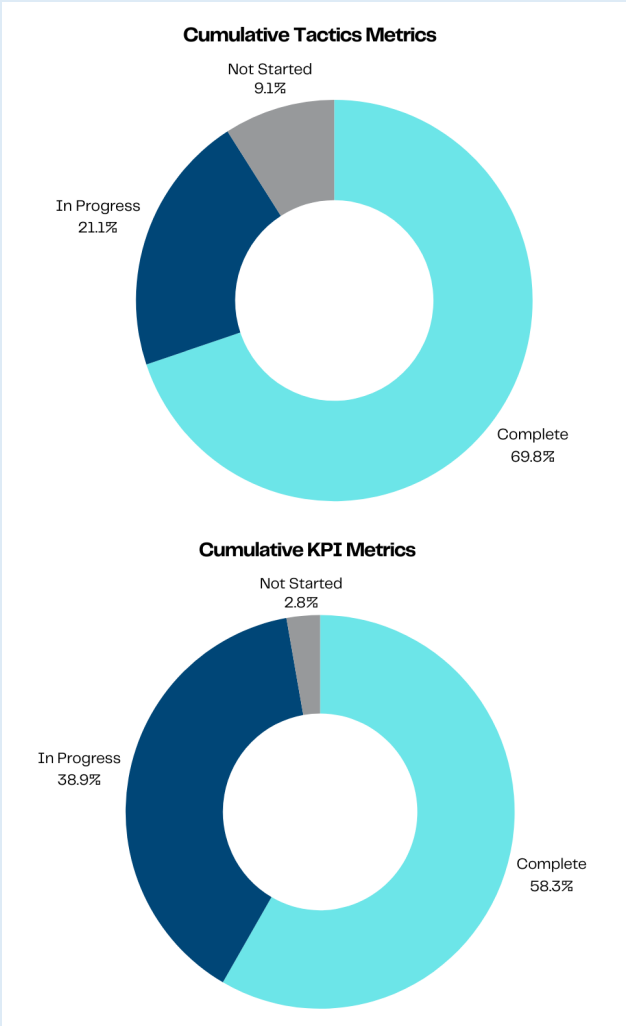
In November 2022, the HOPA Board of Directors approved a comprehensive three-year strategic plan spanning from January 2023 to December 2025. The resulting framework has guided the work of HOPA for the last two years. As we are entering the final year of our three-year plan, I am honored to have the opportunity to provide our members with an update on our progress as well as our plans for the future.

Since January 2023, HOPA Board, committees, and staff have continued to move the organization forward. We have seen tremendous growth on our collaborations and partnerships, mentorship and professional development, diversity, equity, and inclusion, workforce initiatives, cancer-related quality work, advocacy and awareness, and of course, our first-in-class education. To date, we have completed a cumulative total of 69% of all implementation tactics since January 1, 2023, and 58% of all cumulative Key Performance Indicators (KPIs).

Integrating strategic plan tactics into HOPA's standard operating procedures (SOPs) ensures that daily activities align with the organization's overall goals and objectives and that daily operations contribute to the achievement of long-term strategic objectives. More than 15% of our strategic plan tactics are now standard operation procedures.

As we focus on the future, I am pleased to announce that HOPA has engaged a strategic planning firm to assist with the development of our 2026-2029 strategic plan and I encourage you all to participate in surveys or focus groups, if called upon.

I look forward to seeing you in Portland!



"Crushing it": Venetoclax Oral Formulation Alternatives

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Drug development is crushing it in the oral chemotherapy world! There are now over 100 oral oncology drugs approved by the United States Food and Drug Administration.[1] In comparison to intravenously administered medications, oral dosage forms are attractive options for patients due to relative ease of administration and less time in the clinic setting. Unfortunately, more than 50% of patients experience dysphagia during their cancer treatments due to the tumor itself or as a side effect of treatment.[2] This leads to difficulty maintaining adherence to oral chemotherapy.[3] Despite the growth in the development of oral oncology drugs, there remains a gap in knowledge regarding administration of these agents in patients that are unable to tolerate solid oral formulations. Evidence is lacking in extemporaneous compounding of FDA approved oral dose formulations and the effect on safety, efficacy, and bioavailability. This shift towards oral chemotherapy drugs and adherence highlights the need to assess the safety and feasibility of different oral formulation administration methods for patients unable to swallow solid oral formulations.[1]

"Despite the growth in the development of oral oncology drugs, there remains a gap in knowledge regarding administration of these agents in patients that are unable to tolerate solid oral formulations."

Venetoclax is an orally bioavailable, potent, and selective B cell lymphoma (BCL-2) inhibitor currently approved in the treatment of multiple advanced hematologic malignancies including chronic lymphocytic leukemia (CLL) and newly diagnosed acute myeloid leukemia (AML).[4] Investigation is also ongoing in other disease states, including hematologic malignancies and solid tumors in pediatric patients. Venetoclax is available as an orally administered tablet, and the product labeling does not provide any insight on alternative administration routes, thus limiting its use in patients unable to take medications orally.[4]

Venetoclax is currently available as 10, 50, and 100 mg film-coated tablets with approved doses ranging from 400 – 600 mg daily.[4] The 100 mg tablet is the most commonly utilized strength; however, it is a relatively large oblong shaped tablet, which can be difficult to swallow. The lower-strength 10 mg and 50 mg tablets are smaller in size and may be preferred in patients with difficulty in swallowing larger tablets.[5] Based on the biopharmaceutical classification system (BCS), used in drug discovery and development, venetoclax is a highly lipophilic drug with low aqueous solubility which presents challenges for oral formulation development. Currently, the tablets are manufactured by amorphous solid dispersion technology to enhance drug dissolution and bioavailability.[3] Venetoclax is recommended to be taken with food due to a 3-5 fold increase in bioavailability when taken with food compared to on an empty stomach.[5] Due to the oncology patient population having increased potential for dysphagia and potential future indications in the pediatric population, the effects of crushing venetoclax on bioavailability are important clinical questions.

An open-label, randomized, 3-way crossover study was conducted to assess the bioavailability of crushed and finely ground tablets of venetoclax relative to whole tablets. Fifteen healthy female participants were randomly assigned in equal numbers to 3 sequence groups. Each group contained 5 participants who were planned to receive a single dose of 1 of the 3 regimens in each period. Participants were confined to the study site and supervised for 15 days total. Venetoclax was administered orally on day 1 of each period with a 5-day washout between each period as the half-life of venetoclax is less than 24 hours. The 100 mg tablet was selected for this particular study as it is the highest dosage strength available and the most commonly used dosage unit. A manual pill crusher was utilized to crush each 100 mg tablet individually for the crushed regimen. An automated pill crusher was utilized to prepare the ground tablet regimen. Each tablet was then transferred to an amber vial and stored at room temperature prior to administration. On dosing days, participants took the crushed, ground, or whole tablets by mouth within 30 minutes of breakfast followed by a glass of water. Blood samples were collected prior to dosing (0 hours) and at 1, 2, 4, 6, 8, 10, 12, 24, 48, and 72 hours after dosing in each study period for venetoclax assays. Plasma concentration-time data was used to derive the maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}). The mean plasma concentration-time profiles for crushed, ground, and whole venetoclax tablets showed comparable exposures over time for each regimen. All 3 regimens had a similar T_{max} of 6 hours. Area under the curve exposures for crushed and finely ground tablets met bioequivalence criteria.[3]

Badawi, et al. conducted three phase I, open-label, randomized, crossover studies (studies 1, 2, 3) to evaluate the bioavailability of various formulations of venetoclax, assess the interchangeability of the lower-strength tablets, and support the development of oral powder formulations. In these studies, the lower-strength tablets and oral powder formulations were compared to the 100 mg tablet. Study 1 assessed the bioavailability of film-coated tablets with strengths of 10, 50, and 100 mg at a dose of 100 mg

under low-fat conditions. Study 2 compared the bioavailability of two oral powder formulations to the 100 mg tablet under high-fat conditions. This study also evaluated the effect of a high-fat meal on the bioavailability of the oral powder formulation at a dose of 100 mg. Study 3 characterized the effect of different dosing vehicles on the bioavailability of the oral powder formulations when consumed with a moderate-fat meal. Water was used as the reference vehicle, and other vehicles included apple juice, apple sauce, and yogurt. Overall, this study concluded that there are multiple viable options for venetoclax administration. The 10 and 50 mg tablets are bioequivalent to the larger 100 mg tablets; therefore, this confirmation of interchangeability allows patients to use multiple smaller tablets if they have difficulty swallowing the larger 100 mg tablets. The bioavailability of the oral powder formulations was less impacted by food compared to the tablet. Different vehicles used to administer the oral powder formulations did not impact the bioavailability. The authors concluded that these formulations can be used to deliver a therapeutic dose of venetoclax in adult and pediatric patients.[5]

In an additional clinical trial evaluating safety and efficacy in the pediatric population, for those unable to swallow pills, a venetoclax solution was compounded for administration. This was done by crushing the appropriate number of tablets and dissolving in sterile water to a final concentration of 5 mg/mL. Compounding occurred in an oral hazardous compounding hood. Each dose was dispensed in an oral syringe. After administration via nasogastric (NG) tube, each syringe was then rinsed with an additional 5-10 mL of sterile water and administered via NG tube to ensure full dose delivery. Stability of the compounded dose was considered to be one hour once dissolved.[6]

There remains a gap in knowledge regarding the use of liquid formulations or alternative routes of administration of oral oncology drugs. Reports are slowly materializing in describing manipulation of commercially available solid dosage forms providing insight and guidance to practitioners. Fortunately, there is now some data supporting the crushing of venetoclax tablets showing that it does not change the overall bioavailability in a clinically meaningful way. This information provides a valuable option for patients with swallowing difficulties requiring treatment with venetoclax. In the current era of oral oncology drug development, every attempt should be made to provide each patient the opportunity to "crush" their disease with these available options of administration. ●●

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To B[COP] or not to B[COP]: What A Resident Should Know About Board Certification

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You've survived pharmacy school, your PGY1, and now you're halfway through your PGY2 Hematology/Oncology Pharmacy residency. Four little letters—with potentially big implications—now appear on the horizon: BCOP (Board Certified Oncology Pharmacist). Do you pursue this certification? Do you not? Ultimately the choice is yours, but in this article, we will explore the basics of board certification from the perspective of two BCOP-certified pharmacists and one current PGY2 resident.

What is it?[1]

BCOP indicates that the recipient has earned the Oncology Pharmacy Specialty Certification from the Board of Pharmacy Specialties (BPS). It is an optional certification available to licensed pharmacists with the requisite practice experience in the past seven years AND successful passing of the BCOP certification exam. At present, there are currently over 4000 BCOP-certified pharmacists worldwide. Once achieved, the BCOP certification remains active for a period of seven years, after which the pharmacist can recertify by one of two pathways: 1) take the recertification exam, or 2) earn and maintain a certain number of BPS-approved continuing education credits ("BCOP credits") throughout the seven-year certification cycle.

How do I earn it?[1-3]

Step one to earning BCOP is completing the required practice experience—and if you are on track to complete your Hematology/Oncology PGY2, you're already well on your way! Successful completion of a PGY2 residency in Hematology/Oncology satisfies the practice experience eligibility requirement. However, BCOP certification is not restricted to PGY2 residency-trained pharmacists; those with a PGY1 and two years of relevant oncology pharmacy experience, or those with four years of relevant oncology pharmacy experience, are also eligible to apply. Of note, the relevant experience must have been completed in the preceding seven years to be eligible.

Step two is to complete the application, along with payment of the application fee ($600 for first-time applicants, as of time of writing). Of note, some employers may offer reimbursement for testing fees, so if you are considering pursuing BCOP certification, it would be worthwhile to check with your prospective employer to see what support they may be able to offer for initial and continued BCOP fees and requirements.

Step three is to register for the exam. You may have heard your preceptors reference either a 'spring exam' or a 'fall exam' (likely with strong opinions for when to take the exam and why), but BPS has recently transitioned the BCOP exam to a continuous testing model. This new model allows candidates to take their exam at any time during their eligibility period, which, for those who receive their authorization to test (ATT) after January 1, 2025, will be 200 calendar days.

"However, I do truly believe that my BCOP certification has opened doors that would not have otherwise been open without it."

Step four is to take the exam. The exam includes 150 testing items, of which 125 will be scored and 25 will be unscored. BPS publishes the Examination Content Outline, available at https://bpsweb.org/examination-content-outlines/, which outlines the various domains and general content that will be covered on the exam—with breakdowns of how much each domain will comprise on the exam. This is an incredibly valuable tool to direct your efforts while studying and preparing for the exam. There are a multitude of BCOP preparation programs and activities available to help you study, including the BCOP Preparation Course offered by the Hematology/Oncology Pharmacy Association (HOPA) at https://www.hoparx.org/hopa-learn/bcop-prep-recert/.

How do I maintain it?[1]

Once you pass the exam, congratulations! You're a proud BCOP-bearing pharmacist…now what? As you've heard throughout your pharmacy journey, learning is continuous and not a destination; the same is true for your BCOP certification. For those certified after January 1, 2024, you have the choice to recertify by taking the exam again in seven years PLUS earning 20 continuous professional development credits during the seven-year recertification cycle, OR by earning 80 hours of BPS-approved "BCOP credits" from approved providers (either HOPA and/or the American Society of Health-System Pharmacists (ASHP) in collaboration with the American College of Clinical Pharmacy (ACCP)) PLUS 20 continuous professional development credits in that seven-year timeframe. A minimum of 2 hours of "BCOP

credits" and/or continuous professional development credits must be self-reported each year to maintain your active certification in good standing. This again may be different from what you've heard from your preceptors; for anyone who was certified prior to January 1, 2023, the requirement was to either pass the recertification exam or earn 100 "BCOP credits" in the seven-year recertification cycle. The take-home point is nonetheless the same; be sure to stay on top of those requirements from the start of your seven-year cycle.

What we think about it

Marshall Winget, PharmD

As a PGY2 Resident, I see benefit in pursuing board certification. I view it as a dedication to lifelong learning and a commitment to your patients and healthcare teams. It demonstrates that you are well-informed on new information within the oncology specialty. Also, as a resident and learner, I've been appreciative of preceptors who have kept up board certification to better educate their learners. I seek to pursue BCOP credentials following the completion of my residency in order to do just that. I feel a responsibility to those I serve to keep up with the field of oncology, and BCOP is built for ensuring this.

Marin Abousaud, PharmD, BCOP

I believe it's beneficial to obtain and maintain BCOP certification. With hematology/oncology being a rapidly evolving field, it's important as hematology/oncology pharmacists to stay up to date with the latest data and information to better serve our patients and be valuable members of the healthcare team. However, it can be expensive to obtain and maintain this certification so it's certainly a factor to keep in mind. Try to negotiate with future employers to cover some of the costs of this certification if possible. Costs include the study material to prepare for the exam, the exam, and the additional cost each year to obtain credits, either through attending conferences such as HOPA or BCOP study bundles. It can also be difficult because you must achieve a passing score on each BCOP certification course or else it will not count as credit. I'd recommend if you plan on pursuing BCOP certification, find a study group to work on the educational activities with and ensure you have a plan in place to complete BCOP hours on an annual basis to reach the requirement by the end of seven years.

Alexis Kuhn, PharmD, BCOP—BPS Oncology Specialty Council Member

As a current member of the Oncology Specialty Council, I'll admit that I am certainly biased in favor of pursuing BCOP certification. However, I do truly believe that my BCOP certification has opened doors that would not have otherwise been open without it. It provides valuable recognition and common ground with pharmacy peers, as well as physician colleagues who similarly pursue and maintain their own board certifications. Furthermore, as one who practices in a relatively niche area of oncology pharmacy (pediatrics), the ongoing recertification activities really do keep me abreast of what is happening in other areas of oncology—and what may trickle down to pediatrics in the coming years. I do think that it has enhanced my ability to provide high quality patient care, and I don't hesitate to recommend BCOP to any oncology residents who are considering it. ●●

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Belantamab Mafodotin's Triumphant Return: Breakthrough Results from DREAMM-7 and DREAMM-8 Trials for Relapsed/Refractory Multiple Myeloma

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Belantamab mafodotin (Blenrep) is a B-cell maturation antigen (BCMA) targeting humanized monoclonal antibody drug conjugated to microtubule-disrupting agent, monomethyl auristatin F (MMAF), via a stable, protease-resistant linker.[1] BCMA is a cell-surface receptor expressed on multiple myeloma, plasma, and mature B lymphocyte cells.[2] The anti-BCMA moiety binds MMAF to BCMA-expressing multiple myeloma cells, inducing apoptosis via G2/M phase cellular arrest. It also enhances antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis to induce immunogenic cell death. It was the first BCMA targeting agent to be FDA approved on the market.

Initial Approval of Belantamab Mafodotin

The Food and Drug Administration granted accelerated approval to belantamab mafodotin on August 5, 2020, for adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent as a monotherapy. The decision was made based on the results of the DREAMM-2 study.[3,4] In this open-label phase 2 trial[1], belantamab mafodotin monotherapy was evaluated in adult patients whose multiple myeloma was refractory to multiple agents, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. Patients received either belantamab mafodotin, 2.5 mg/kg or 3.4 mg/kg intravenously, once every 3 weeks, until disease progression or unacceptable toxicity. Overall response was observed in approximately one-third of patients. The approval was granted for a dose of 2.5 mg/kg as an intravenous infusion once every 3 weeks. Comparing to 3.4 mg/kg dose, the 2.5 mg/kg dose had the similar efficacy and more favorable safety profile including less frequent dose modifications and less thrombocytopenia, bleeding, neutropenia, and infections.[1] The most common adverse reactions observed in ≥20% of study participants were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. Common grade 3/4 adverse events reported included keratopathy, thrombocytopenia, and anemia. Keratopathy was of significant concern, resulting in the inclusion a Boxed Warning in the prescribing information detailing the risk for corneal epithelium changes and alterations in vision (i.e., severe vision loss, corneal ulceration, and symptoms such as blurred vision and dry eyes).[4] For patients on therapy, the prescribing information recommended that ophthalmic exams be conducted at baseline, before each dose, and promptly for worsening symptoms. Because of the ocular toxicity risk, belantamab mafodotin was only available through a restricted program, the BLENREP Risk Evaluation and Mitigation Strategy (REMS). The exact mechanism behind ocular toxicity is unknown, but it is not uncommon with antibody-drug conjugates (ADC). Toxicity may be related to the uptake of the ADC into actively dividing epithelial cells in the basal epithelial layer of the cornea.[5]

"Since the initial approval of belantamab mafodotin, other BCMA-directed agents have been incorporated in the multiple myeloma treatment algorithm..."

Market Withdrawal of Belantamab Mafodotin

In November 2022, GlaxoSmithKline (GSK) announced that belantamab mafodotin would be withdrawn from the market due to the drug's inability to demonstrate progression free survival (PFS) benefit in the DREAMM-3 trial. This phase 3, open-label, randomized study enrolled patients who had received two or more previous lines of therapy, including an immunomodulatory agent and proteasome inhibitor. A total of 325 patients were included to receive either belantamab mafodotin (218 patients) or pomalidomide/dexamethasone (107 patients). Median PFS was found to be 11.2 months compared to 7 months (HR 1.03; 95% CI, 0.72 to 1.47), respectively.[3,6] After belantamab mafodotin's removal from the market, the FDA allowed patients already enrolled in the REMS program to continue on treatment. Even though belantamab mafodotin was not found to be better than standard of care, the safety data was consistent to previous findings.

The Comeback of Belantamab Mafodotin

After its market withdrawal, belantamab mafodotin was studied for use in combination with other standard of care agents in the DREAMM-7 and DREAMM-8 studies. Both phase 3 clinical trials provide further evidence of belantamab mafodotin's utility as second line or greater treatment for relapse/refractory multiple myeloma.

DREAMM-7 is a phase 3, open-label, randomized trial, which compared belantamab mafodotin, bortezomib, and dexamethasone (BVd) to daratumumab, bortezomib, and dexamethasone (DVd), in patients with progression of multiple myeloma after at least one line of therapy.[6] A total of 494 patients were randomized to either receive BVd (243 patients) or DVd (251 patients). At a median follow-up of 28.2 months, median PFS was 36.6 months for the BVd

group and 13.4 months for the DVd group (HR 0.41; 95% CI 0.31 to 0.53; P-value <0.001). Overall survival (OS) at 18 months was 84% in the BVd group and 73% in the DVd group. BVd was associated with greater depth of response with doubling CR rate and more than double the MRD negativity rate (sensitivity of 10^{-5}) of DVd in 25% of the patients in the BVd group and 10% in the DVd group (p-value <0.0001). Grade 3 or higher adverse events occurred in 95% of the patients in the BVd group and 78% of those in the DVd group. Across both treatment groups, the most common adverse events were cytopenia and infections. Ocular events were more common in the BVd group (79% vs. 29%) and mainly managed with dose modifications. In the event of toxicity, belantamab mafodotin was either dose reduced from 2.5 mg/kg to 1.9 mg/kg or delayed. 93% of worsening visual acuity events resolved. The authors concluded that BVd therapy compared to DVd demonstrated a significant PFS benefit among patients who had relapsed or refractory multiple myeloma after at least one line of therapy.

DREAMM-8 is a phase 3, open-label, randomized trial, which compared belantamab mafodotin, pomalidomide, and dexamethasone (BPd) to pomalidomide, bortezomib, and dexamethasone (PVd), in lenalidomide-exposed patients with relapsed or refractory myeloma after at least one line of therapy.[7] In the BPd group, patients received 28-day cycles of belantamab mafodotin (2.5 mg/kg intravenously on day 1 of cycle 1 and 1.9 mg/kg on day 1 with each subsequent cycle) combined with pomalidomide and dexamethasone. A total of 302 patients were randomized; 155 were assigned to the BPd group and 147 to the PVd group. At a median follow-up of 21.8 months, the 12-month estimated PFS with BPd was 71% (95% CI 63 to 78), as compared with 51% (95% CI, 42 to 60) with PVd (HR for disease progression or death, 0.52; 95% CI, 0.37 - 0.73; P <0.001). Currently OS data is immature. However, OS in the interim analysis did not reach significance. The percentage of patients with partial response or better was 77% (95% CI, 70 to 84) in the BPd group and 72% (95% CI, 64 to 79) in the PVd group. Complete response or better was observed in 40% (95% CI, 32 to 48) in the BPd group and 16% (95% CI, 11 to 23) in the PVd group. Grade 3 or higher adverse events occurred in 94% of the patients in the BPd group and 76% of those in the PVd group. The most frequently reported adverse events in the BPd group were blurred vision, dry eye, and foreign-body sensation in the eyes; in the PVd group neutropenia, thrombocytopenia, and anemia were the most commonly reported. Ocular events occurred in 89% of the patients who received BPd (grade 3 or 4 in 43%) and 30% of those who received PVd (grade 3 or 4 in 2%). Similarly to DREAMM-7, ocular toxicities in the BPd group were managed with belantamab mafodotin dose modification. Ocular events led to treatment discontinuation in 9% of the patients in the BPd group and no patients in the PVd group. The authors concluded that among lenalidomide-exposed patients with relapsed or refractory myeloma, BPd demonstrated a significantly greater benefit than PVd with respect to PFS, as well as deeper, more durable responses.

Table 1. DREAMM-7[6] and DREAMM-8[7] Studies Summary

	DREAMM-7		DREAMM-8	
	Belantamab mafodotin, Bortezomib, and Dexamethasone **(BVd)** n=243	Daratumumab, Bortezomib, and Dexamethasone **(DVd)** n=251	Belantamab mafodotin, Pomalidomide, and Dexamethasone **(BPd)** n=155	Pomalidomide, Bortezomib, and Dexamethasone **(PVd)** n=147
Median follow up	28.2 months		21.8 months	
Median PFS	36.6 months	13.4 months	NR	12.7 months
	HR=0.41; 95% CI, 0.3- 0.53; P <0.001		HR=0.52; 95% CI, 0.37 - 0.73; P<0.001	
12-months estimated PFS	--	--	71%	51%
OS at 18 months	84%	73%	--	--
OS at 12 months	--	--	83%	76%
ORR	83%	71%	77%	72%
CR	35%	17%	40%	16%
CR MDR negativity	25%	10%	24%	5%
VGPR	66%	46%	64%	38%
VGPR MRD negativity	38%	17%		
Grade 3 or higher adverse events	95%	78%	94%	76%
Infection	70%	67%	82%	68%
Ocular Events	79%	29%	89%	30%
Discontinuation	26%	15%	15%	12%
Ocular events led to treatment discontinuation	9%	0	9%	0

CR= complete response; HR= hazard ratio; MRD= minimal residual disease; NR= not reached; ORR= overall response rate; OS= overall survival; PFS= progression-free survival; VGPR= very good partial response

The PFS benefit observed in the DREAMM-7 and DREAMM-8 studies demonstrates favorable efficacy outcomes with belantamab mafodotin combination therapy in the second-line setting. DREAMM-7 is the first trial to demonstrate superiority over a daratumumab-based triplet combination in this line of therapy. Though ocular toxicity remains a concern, harm can be mitigated with dose modifications as demonstrated by both trials. Among DREAMM-7 and DREAMM-8, dose delays attributed to ocular toxicity occurred in 78% and 75% of patients; belantamab mafodotin discontinuation occurred in 9% and 8% of patients, respectively.[9,10] And yet, despite less frequent administrations, belantamab mafodotin was still able to demonstrate its efficacy as a part of a combination regimen.

Place in Therapy/Future Direction

Triplet and quadruplet regimens including proteasome inhibitors, immunomodulators, and anti-CD38 antibodies remain the standard of care treatment for patients with newly diagnosed multiple myeloma.[3,8] These regimens are associated with prolonged PFS and OS; however, most patients will relapse and require alternative therapies. In the current Multiple Myeloma NCCN Guidelines, belantamab mafodotin is listed as useful in certain circumstances (if available through GSK's compassionate use program) after at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.[3] Since the initial approval of belantamab mafodotin, other BCMA-directed agents have been incorporated in the multiple myeloma treatment algorithm, including two bispecific t-cell engagers (BiTEs), elranatamab (Elrexfio) and teclistamab (Tecvayli); and two chimeric antigen receptor T cells (CAR-T) idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti). Among these agents, some are recommended as earlier lines of therapy.[9] If belantamab mafodotin is approved, its incorporation as a second line agent may complicate the sequencing of BCMA-directed therapy. Subgroup analyses from CARTITUDE-4[10] and KarMMa-3[11] suggest BCMA-directed CAR-T works better in patients without prior BCMA-directed agent exposure; this is due to the theoretical concern that prior exposure to BCMA-directed agents may induce point mutations in the antigen, preventing the binding of later line therapies such as CAR-T and BiTE therapies.[12] However, in the DREAMM-7 study, 36 patients who progressed had detectable soluble BCMA at baseline and at the time of disease progression in the post hoc analysis. This suggests the possibility that patients treated with BCMA-targeting therapy may not experience BCMA target loss similar to what was previously reported.[13] A potential area of future research is whether belantamab mafodotin, similar to many other ADCs across different tumor types (e.g. fam-trastuzumab deruxtecan for breast cancer), can maintain its activity in patients with prior exposure to BCMA-targeted therapy including BiTEs and/or CAR-T therapy. This will be fundamental for guiding clinicians in sequencing available agents in the multiple myeloma treatment paradigm.

DREAMM-7 and DREAMM-8 are two significant phase 3 clinical trials that provide further evidence of the utility of belantamab mafodotin in second-line or greater relapse/refractory multiple myeloma. We look forward to incorporating this evidence in future updates to the guidelines. ●●

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Greener Pastures on the Horizon for Medicare Patients

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It's an all too familiar scenario for many of us. You're called to discuss the initiation of an oral cancer therapy with a patient. Maybe it's a rare mutation that the cancer harbors and a newly approved oral oncolytic is the perfect treatment for this patient of yours. Compared to the standard-of-care, this agent might have improved response rates, survival outcomes, and even patient-reported quality of life. Breakthroughs in years of research have culminated in this moment where you, your team, and the patient are all excited to celebrate. Your team provides education and instructions on how to take the medication and the prescription gets scurried off to the specialty pharmacy for dispensing. In the days that pass, prior authorization forms and even appeals have been filled out with the ultimate greenlit "APPROVED" outcome on the form and it's a sigh of relief. But disappointment resurfaces as the insurance claim returns with some egregious four-figure number that no one can realistically expect a patient to pay. The patient and/or oncologist might scoff, saying "well, they told me it was approved – this can't be right!". The excitement that once electrified the air has just as easily dissipated, replaced with shock and a sense of hopelessness.

"As pharmacists and technicians, we are intimately tied to the access, acquisition, and dispensing of medications for patients."

The Inflation Reduction Act, initially passed in August 2022, was a historic piece of legislation that reduced the federal deficit to combat inflation. Some of its key provisions included pledges to lower carbon emissions and cleaner energy, but financial relief for millions of Americans with Medicare was especially groundbreaking. For many, the structure of out-of-pocket (OOP) costs of prescription medications is an alphabet soup of confusing terms and numbers. Between premiums, deductibles, tier lists, copayments, coinsurance, and the coverage gap, patients at the pharmacy would be left in disbelief over the pricing of prescriptions that controlled the growing number of chronic illnesses that had befallen them. Oncology patients have been especially affected as many therapies aimed at fighting cancer were developed as oral treatments that were self-administered at home. In the clinic, my colleagues and I are often asked the same questions by patients, nurses, physicians, and advanced practice providers: "why is the copay so high?" and "what alternatives can we prescribe instead?".

As a refresher, it might be helpful to review the different costs commonly associated with Medicare prescription drug coverage. Premiums include the monthly fee of carrying a Part D plan. The deductible is the total amount that needs to be paid each year by the subscriber before the Medicare plan starts paying its share of costs. In 2024, this amount was limited to $545 for Medicare plans[1]. Coinsurance and copayments are the percentage and set dollar amounts, respectively, that subscribers pay for covered medications after the deductible is met. Preferred and generic medications may be assigned a lower tier (and cost less for subscribers) than non-preferred and branded medications. Additionally, certain plans may offer lower costs to subscribers if they are filled at a certain pharmacy or network of pharmacies. The coverage gap or "donut hole" is the next phase of coverage once patients and plans have spent a total of $5,030 in 2024 on covered medications[1]. During this phase of coverage, 25% of the cost of covered medications are paid by the Medicare subscriber and this continues until a total of $8,000 of OOP spending is paid. For brand-name medications, manufacturers provide a 70% discount on the cost of the medication, while your plan pays 5% and the patient pays the remaining 25%, plus any other dispensing fees. For generic medications, the plan will pay 75% while the patient pays 25%. The costs that count towards the $8,000 annual OOP spending includes deductibles, coinsurance, and copayments, as well as the manufacturer discounts on branded medications paid for covered drugs in the coverage gap[1].

Beginning in 2025, OOP prescription drug costs for patients will be further limited to $2,000 annually[1]. This represents an even greater effort to limit OOP spending for a population with growing health care costs and fixed incomes. Additionally, Medicare will also implement cost smoothing, aimed at reducing the acute burden of expensive prescription medications. Under the Medicare Prescription Payment Plan (MPPP), any Medicare Part D recipient can opt into a service that distributes OOP costs of covered prescription medications into monthly payments. Patients will be required to opt-in for this benefit and can do so during Open Enrollment. They can also opt-in at any time during the plan year without penalty. If patients opt-in during the plan year, plan providers are required to process the request within 24 hours to facilitate a timely initiation or maintenance of therapy. Importantly, the costs are not smoothed over the 12 months, but over the remaining number of months in the calendar year relative to when costs are incurred. If multiple medications are added to the MPPP, the monthly costs will be reconfigured to account for new or removed medications to the program. Plan providers will be responsible for reimbursing pharmacies upfront for any Medicare Part D recipient that has opted-in for the MPPP. Additionally, they would be required to notify pharmacies to inform patients if the OOP cost of a single covered medication exceeds $600 to encourage enrollment.

It's undeniable that the upcoming changes coming to Medicare in 2025 will greatly benefit a large proportion of our cancer patients. Cancer statistics and trends reveal that the median age of cancer diagnosis in the United States is 67 and that the age-adjusted cancer rates in patients 65 and older is nearly 20 times that of

patients younger than 50 years of age[2]. For some patients, turning 65 includes transitioning to a fixed income that is often lower than what they may have earned in previous years. The growing cost of healthcare and the increasing number of comorbidities means that healthcare-related costs continue to climb for patients. With these reforms to Medicare, prescription drug costs will be capped and can be distributed over multiple months to ease the burden of healthcare costs.

The Inflation Reduction Act also enabled Medicare to negotiate prices directly with drug companies, particularly for single-sourced branded medications. The Department of Veterans Affairs (VA) has an established practice and history of negotiating medication prices with drug companies. In fact, the U.S. Government Accountability Office (GAO) released a study in 2020 showing that unit prices paid by the VA were 68% lower for the 203 evaluated generic medications and 49% lower for the 196 brand-name drugs compared to Medicare prices[3]. The passage of the Inflation Reduction Act provides Medicare the power to negotiate costs that can reduce the overall expenditures Part D patients incur with covered medications. In doing so, the Biden administration identified and established the Maximum Fair Prices of ten medications covered under Medicare Part D, which is set to take effect on January 1, 2026. These medications include Januvia, Farxiga, Fiasp products, Novolog products, Jardiance, Enbrel, Stelara, Xarelto, Eliquis, Entresto, and Imbruvica. The negotiations yielded a discount that ranged between 39% (for Imbruvica) and 79% (for Januvia) compared to the list prices for a 30-day supply of the medication. It is expected that if the negotiated prices had been in effect in 2023, an estimated $6 billion would have been saved in net covered prescription costs. While cancer therapies have very limited inclusion in the initial rollout of the negotiations, there are more opportunities in the future. Still, many of our older patients with cancer will undoubtedly take high-cost brand-name medications and so the impacts of these initial price negotiations will have a broad scope when the program is implemented in 2026.

As pharmacists and technicians, we are intimately tied to the access, acquisition, and dispensing of medications for patients. Many of us work in direct patient care, be it in a clinical or operational role. It's important that we disseminate this information to those we work with and to the patients we serve daily. As part of my own practice, I try to encourage patients to be an active player in their own health care. While I may not always have the capacity to access the details of a patient's prescription drug formulary, I do encourage patients to do so on their own. In helping them navigate their online accounts and formularies, conversations inevitably come up about why costs continue to rise and how something needs to be done. It's often under these circumstances where I encourage them to talk to their elected officials to push for reducing healthcare-related costs for every patient and to share their own personal stories. Big or small, one or one thousand: we all have a voice and it's vital that we use it. In a not-too-distant future, it is my earnest hope that the joys of medical breakthroughs can be fully realized for what they are and that financial status or "the right kind of drug plan" are not the primary determinants of who does and does not have access to care. ●●

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Impact of Weight and Creatinine Adjustments on the Accuracy of Cockcroft-Gault Equation in Hematopoietic Cell Transplant Patients

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Background

Patients receiving hematopoietic cell transplant (HCT) must undergo vital organ function evaluation prior to transplant to confirm eligibility and tailor pharmacotherapy. Renal function is an essential component of the evaluation process to confirm eligibility for HCT. Renal function impacts the conditioning regimen, graft-vs-host disease (GVHD) prophylaxis, non-relapse mortality (NRM) and overall mortality.[1]

The Cockcroft-Gault (CG) equation was originally developed to estimate renal function utilizing actual body weight from male patients who were mainly of normal weight.[2] Since then, there have been many studies analyzing the most precise weight calculation to be utilized within the CG in the pursuit of accurately estimating renal function. Currently, there is a discordance of evidence regarding which of the various weight adjustments for the CG equation provides the truest assessment of renal function.[3,4,5,6] Additionally, there is limited evidence regarding the most accurate method of estimating creatinine clearance (CrCl) within the pre-HCT patient population and no studies exist that evaluate the weight utilized within the CG equation in HCT patients.

"Our study with the utilization of ADjBW0.4 provided the highest correlation, least bias, and greatest accuracy compared to mCrCl."

Methods

A single center, retrospective analysis was completed at Moffitt Cancer Center to evaluate the different weight and serum creatinine (SCr) adjustments utilized within the CG equation for assessment of renal function.[7] This study included adult patients who underwent pre-transplant renal function assessment and completed a 24-hour urine creatinine collection prior to HCT from January 1, 2001, through December 30, 2012. Patients were excluded if they did not have a recorded SCr or 24-hour urine creatinine, had a urine collection < 500 mL, or were missing a documented height or weight. The primary endpoint was evaluation of the CrCl estimation with CG compared to measured CrCl (mCrCl) utilizing total body weight (TBW), ideal body weight (IBW) and adjusted body weight ($ADjBW_{0.4}$). $ADjBW_{0.4}$ was calculated as [IBW + 0.4 x (TBW – IBW)]. Each patient included in the study had a pre-transplant 24-hour urine creatinine clearance performed to be used as the mCrCl. For the primary analysis, all patients with TBW > IBW were given an adjusted body weight; however, for the sub analysis of $AdjBW_{0.4}$ at specific weight thresholds (≥ 120% and ≥ 140% IBW), only patients who met these pre-defined thresholds were included. For patients with TBW < IBW, TBW was utilized. Correlation between estimated CrCl with the CG equation and mCrCl was tested through Pearson's correlation coefficient (r). Equation accuracy was defined as the percentage of patients with estimated CrCl within 30% of the actual mCrCl, further referred to as percent within range (PWR). This pre-defined threshold was cited in previous studies as sufficiently accurate for clinical decision making.[3] Equation bias was evaluated through mean difference (MD) calculations between estimated CrCl and mCrCl. The 95% confidence intervals were calculated by using the exact binomial distribution. A two-sided p-value of ≤ 0.05 was considered statistically significant. Analyses were conducted utilizing SAS 14.3 (Cary, NC) and Excel. Secondary endpoints included determination of the most accurate weight for the CG equation in autologous and allogeneic transplants, HCT indication, gender, age group (≥ 60, < 60 years old), chronic kidney disease (CKD) stage and Karnofsky performance status (KPS). Additional secondary analyses included determination of the impact of rounding SCr up to pre-defined thresholds in patients ≥ 60 years old and the accuracy of $ADjBW_{0.4}$ at pre-specified cutoffs of ≥ 120% and ≥ 140% IBW.

Results

Seven hundred and forty-two patients were included. Of those patients, 56% were male, 29% were sixty years or older, and 61% received an autologous transplant (Table 1). Eighty-eight percent of patients included had CKD stage 2 or less. Correlation coefficients for the primary outcome between TBW, IBW, and $ADjBW_{0.4}$ were similar (r = 0.801, 0.790, and 0.812 respectively). The mean differences for each estimation from mCrCl were +6.57 mL/min (95% CI 3.92 to 9.21) for TBW, -18.03 mL/min (95% CI -20.40

Table 1. Baseline characteristics: underweight (BMI ≤18.5), normal weight (BMI 18.6-24.9), overweight (BMI 25-29.9), obese (BMI 30-39.9), morbidly obese (BMI ≥40) †Scr = serum creatinine ‡CrCl = calculated creatinine clearance §Chronic Kidney Disease Stage ¶ Not all patients had KPS score available, total is listed per group

	All patients (N=742)	Underweight (N=9)	Normal weight (N=215)	Overweight (N=281)	Obese (N=202)	Morbidly obese (N=35)
Male, N (%)	418 (56%)	3 (33%)	92 (43%)	180 (64%)	130 (64.3%)	13 (37%)
Age (years)	51 ± 13.4	40 ± 15.2	50 ± 14.1	51 ± 12.9	52 ± 13.2	46 ± 11.76
Age ≥ 60, N (%)	217 (29%)	1 (11%)	63 (29%)	88 (31%)	61 (30%)	4 (11%)
Height (cm)	170.4 ± 10.25	166.1 ± 8.36	168.3 ± 10.18	171.7 ± 10	171.5 ± 9.91	167.8 ± 11.86
Weight (kg)	82.5 ± 20.44	47.5 ± 5.23	63.8 ± 9.99	80.7 ± 10.58	99 ± 14.04	124.4 ± 20.47
BMI (kg/m²)	28.2 ± 6	17.2 ± 0.93	22.4 ± 1.69	27.3 ± 1.4	33.5 ± 2.61	44.1 ± 5.91
S_{cr} (mg/dl)†	1.01 ± 0.61	0.78 ± 0.17	0.99 ± 0.62	0.98 ± 0.45	1.09 ± 0.79	1 ± 0.53
CrCl <30 mL/min‡, N (%)	19 (2.6%)	0	11 (5%)	3 (1.1%)	5 (2.5%)	0
CrCl <60 mL/min‡, N (%)	79 (11%)	3 (33%)	44 (20%)	20 (7.1%)	12 (6%)	2 (5.7%)
Allogeneic transplant, N (%)	287 (39%)	3 (33%)	97 (45%)	102 (36%)	70 (35%)	15 (43%)
Autologous transplant, N (%)	455 (61%)	6 (67%)	118 (55%)	179 (64%)	132 (65%)	20 (57%)
Transplant Indication, N (%)						
Leukemia	185 (25%)	3 (33%)	63 (29%)	63 (22%)	47 (23%)	9 (26%)
Lymphoma	154 (21%)	1 (11%)	34 (16%)	60 (21%)	51 (25%)	8 (23%)
Multiple Myeloma	322 (43%)	3 (33%)	85 (40%)	133 (47%)	86 (43%)	15 (43%)
Solid tumor	26 (3.5%)	2 (22%)	9 (4.2%)	9 (3%)	6 (3%)	0
Myeloproliferative	46 (6.2%)	0	19 (8.8 %)	15 (5%)	9 (4.5%)	3 (8.6%)
Aplastic Anemia	9 (1.2%)	0	5 (2.3%)	1 (0.4%)	3 (1.5%)	0
CKD stage§, N (%)						
1-2	650 (88%)	9 (100%)	184 (86%)	253 (90%)	175 (87%)	29 (83%)
3	68 (9.2%)	0	21 (10%)	23 (8.2%)	20 (10%)	4 (11%)
4-5	24 (3.2%)	0	10 (4.7%)	5 (1.8%)	7 (3.5%)	2 (5.7%)
KPS Score¶, N (%)						
90-100	340/511 (67%)	3/5 (60%)	88/139 (63%)	134/195 (69%)	106/153 (69%)	9/19 (47%)
≤ 80	171/511 (33%)	2/5 (40%)	51/139 (37%)	61/195 (31%)	47/153 (31%)	10/19 (53%)

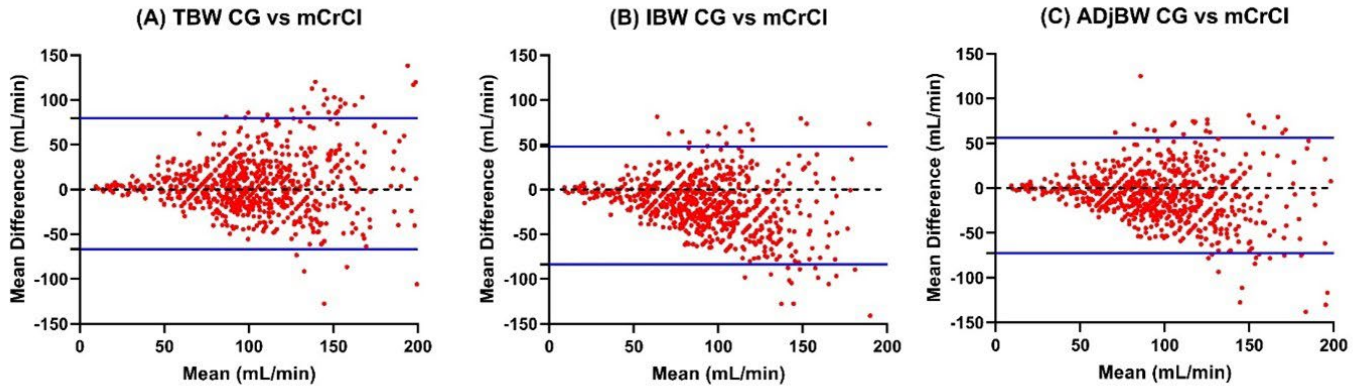

Figure 1. Bland Altman plots for primary outcome (A) Actual body weight, TBW (B) Ideal body weight, IBW (C) Adjusted Body Weight, $ADjBW_{0.4}$

to -15.66) for IBW, and -8.19 mL/min (95% CI-10.5 to -5.88) for $ADjBW_{0.4}$ (Figure 1). All mean differences were significantly different from mCrCl ($P < 0.0005$). $ADjBW_{0.4}$ achieved the highest PWR with 75.5% of values in range compared to IBW with 65.6% and TBW with 72.4%. Analyzing the pre-specified percentage of IBW thresholds, usage of a ≥ 120% IBW threshold to utilize $ADjBW_{0.4}$ produced less bias and greater correlation to mCrCl in comparison to a ≥ 140% IBW threshold. In patients who met TBW ≥ 120% IBW, the correlation to $ADjBW_{0.4}$ was r = 0.807 and mean difference -11.06 mL/min. While TBW ≥ 140% IBW had a correlation to $ADjBW_{0.4}$ 0.771 and mean difference of -11/46 mL/min. At both thresholds, IBW and TBW produced greater bias, and lower correlation compared to $ADjBW_{0.4}$. The benefit seen with $ADjBW_{0.4}$ was generally consistent across subgroup analyses. In patients 60 years and older, rounding SCr up to thresholds of 0.8 mg/dL or 1 mg/dL resulted in less correlation, greater bias, and a lower PWR compared to not rounding.

Discussion

For HCT, accurate renal function assessment is pivotal in the pre-transplant assessment process. Our study with the utilization of $ADjBW_{0.4}$ provided the highest correlation, least bias, and greatest accuracy compared to mCrCl. Total body weight held high correlation but tended to overestimate CrCl, while IBW provided the lowest correlation and greatest bias. In patients ≥120% IBW, use of $AdjBW_{0.4}$ underestimated the patient's CrCl while TBW overestimated CrCl by a similar amount, but $AdjBW_{0.4}$ had higher accuracy. In 2012, Winter and Colleagues analyzed the CG compared to mCrCl in adults admitted to an inpatient hospital. They utilized BMI categories to compare TBW, IBW, $AdjBW_{0.3}$, and $AdjBW_{0.4}$ in CrCl estimations to assess the most accurate weight to utilize.[3] A key difference between our study and the Winter trial, besides our study being specific to pre-HCT patients, is that our measured CrCl was completed within the outpatient setting on more clinically stable patients. This may have increased inaccurate collections but focused on more stable renal function compared to a hospital inpatient population. We acknowledge several limitations in our study including the retrospective nature of the analysis, outpatient 24-hour urine collections leading to risk for interpatient variation in consistency of collection, and patients were assumed to have stable renal function at baseline at the time of 24-hour urine creatinine collection. Additionally, intrapatient variability of serum creatinine values can occur, particularly depending on the time of day drawn.

Conclusion

Amongst patients undergoing HCT, $AdjBW_{0.4}$ was the least biased and most accurate weight to use in the CG equation. Utilizing ≥120% IBW produced less bias and higher accuracy compared to a ≥140% threshold. The practice of rounding low SCr up to 0.8 mg/dL or 1 mg/dL in CG equation did not improve the accuracy of estimating CrCl.

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To Do or Not to Do: The Use of Appetite Stimulants in Cancer Patients

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Background

One of the most prevalent conditions for cancer patients is malnourishment or any alteration in nutrition. Cancer cases have doubled from 1990 to 2017 and are predicted to reach 14 million cases by 2035. Supportive care and survivorship play a big role for these patients during and after therapy. The support from healthcare professionals and loved ones during therapy and after therapy can be life changing.[1] One supportive care issue before and after therapy is nutrition and more specifically malnutrition during therapy due to many causes (see Figure 1).[2] There are no standard of care guidelines for cancer related anorexia or malnutrition and recommendations are very weak in terms of pharmacologic therapy. Instead, the 2017 European Society for Clinical Nutrition and Metabolism nutrition guidelines for patients with cancer recommend to improve nutrition for cancer patients with physical and nutritional modalities and lifestyle changes.[1]

"There is a great deal of controversy on if we should even use appetite stimulating agents at all in cancer patients and research is ongoing."

Anorexia/Cachexia

Anorexia related to cancer is due largely to decreased appetite from disturbances in the central nervous system which leads to nutritional deficiencies. There are other causes of anorexia too, but decreased appetite accounts for 69% of cases. Other factors are dysgeusia which is changes in taste of food (40.3%) and nausea and vomiting which is 31.9% of cases. The formal definition of anorexia is defined as <60% of adequate energy intake for more than 1 week. The impact of nutritional deficiencies is vastly significant as it can affect quality of life, treatment related toxicities and most importantly, patient survival. Malnutrition cannot always be corrected in patients with cancer due to ongoing disease, but early intervention with the right guidance can be monumental.[1,3]

Appetite Stimulants

A review by a cancer researcher and nutrition researcher was published which looked at studies from 1990 to 2020 using PubMed with Medical Subject Heading (MSH) terms of appetite stimulants, anorexia, CACS, orexigenic agents, appetite, cancer. They included 38 studies which involved cannabinoids (megestrol acetate, THC, dronabinol, cannabis extract, THC or nabilone) (10 studies), mirtazapine (4 studies), ghrelin (8 studies) and n-3 fatty acids (16 studies). The outcomes they were searching for in these studies were appetite, energy intake, weight changes or body composition changes and taste alterations in patients with cancer. Each study on its own had different inclusion and exclusion criteria and most of them used weight as a marker or improvement rather than appetite, which is a limitation. However, mirtazapine, cannabinoids and ghrelin showed to have the most promising data and each will be discussed separately in this article.[1]

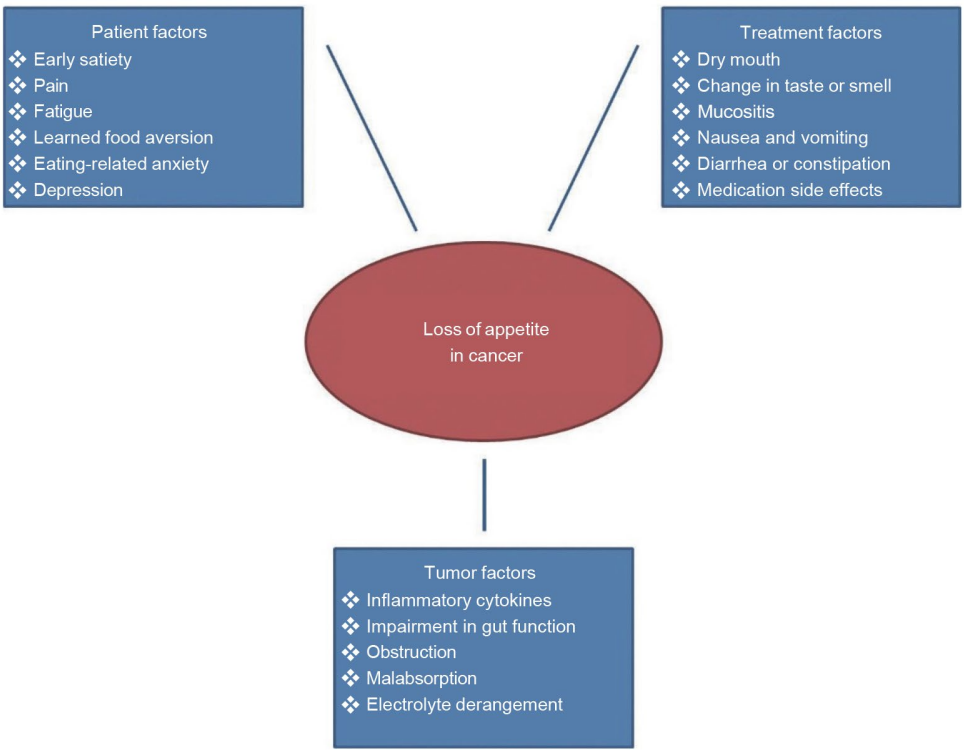

Figure 1. Annals of Palliative Medicine, Vol 8, No 1 January 2019

Cannabinoids

The hypothalamus has CB1 receptors which regulate appetite, weight, and blood pressure. Cannabinoids have effect on increasing appetite stimulation partly by orexigenic effects through inhibition of leptin in the hypothalamus along with inhibiting nausea and vomiting and improving mood. We will not discuss all cannabinoids in this article, but we will focus on dronabinol as it is the most widely

used in cancer patients and then THC and nabilone. There were 7 studies which showed that dronabinol 2.5mg by mouth twice daily increased appetite but there was no statistical significance when dronabinol was compared to placebo or megestrol acetate. However, there are many limiting factors in terms of all studies using different endpoints and markers to document improvement.[1]

Megestrol acetate

Megestrol acetate is a synthetic progestin agonist binding to progesterone receptors which stimulates appetite by decreasing inflammatory cytokines. However, the exact mechanism of action on appetite stimulation is unknown. A systematic review as done with 23 studies that looked at megestrol acetate. It was shown to have weight gain more than increased appetite with a lower side effect profile, but other studies showed no effect on weight. Data is conflicting and there is concern of venous thromboembolic events which is a serious side effect of megestrol acetate along with new-onset diabetes mellitus. Common side effects of megestrol acetate include weight gain, appetite stimulation and fluid retention. As oncology pharmacists, we can help providers with looking at other medications the patient is taking that may increase their risk of VTE events, risk factors such as smoking or past medical history that increases the risk of VTE events to help identify which patients should not be taking megestrol acetate.[3,4,5]

Olanzapine

Olanzapine is an antipsychotic effecting both dopamine and serotonin receptors. Olanzapine has effects on stimulating appetite when used as a long-term agent. There was a randomized controlled trial done in Southern India with locally advanced or metastatic gastric hepatopancreaticobiliary or lung cancer who got olanzapine 2.5 mg orally once daily for 12 weeks vs placebo. Both groups were on similar diets with high protein and caloric foods. The proportion of patients with >5% weight gain after 12 weeks was 60% in the olanzapine group and appetite stimulation was 43% in the olanzapine group vs 13% in the placebo group which was statistically significant with a p value of <0.01. Side effects due to olanzapine were mild and manageable. Future studies are needed, but olanzapine seems to be a promising option for anorexia in chemotherapy patients.[6]

Steroids

There are three corticosteroids that have been some data for the use of appetite stimulation- methylprednisolone, prednisolone and dexamethasone. In general, steroids have a high level of recommendation to increase appetite, but a very weak strength for recommendation due to not having a significant impact on increasing body weight. The duration of use for steroids is also limited due to the side effects of these medications to up to 3 weeks. Long term side effects that have been seen are increase in blood sugar and osteopenia. Dexamethasone has shown to be useful in regaining loss of appetite in lung cancer patients, but not increasing appetite or helping with weight gain. [1]

Hormones and Supplements

There is some evidence and thought behind balancing hormone levels to stimulate appetite. Patients with cancer typically have loss of muscle mass and may have low testosterone levels which make them more prone to sarcopenia. Giving these patients supplemental testosterone enanthate 100mg weekly for 7 weeks can be a form of preserving muscle mass, but this was a small randomized trial of 24 patients with cervical and head and neck cancer. It showed an improvement in weight by 1.3kg on average a week, but no quality of life improvement in terms of strength or performance. External selective androgen receptor modulators, such as Enobosarm, can also aide in promoting appetite, but come with many side effects such as depression, sleep disorders and aggression and is used sparingly. Hormone levels can also fluctuate and time of day and menstrual cycles (for women) will cause different levels. Therefore, hormones are controversial and are not recommended for routine use. Vitamin D deficiency also plays a role with sarcopenia deficiency so it can be beneficial to correct this deficiency as it is reported to cause muscle loss and weakness when there is a prolonged deficiency for type II muscle which is maintained by vitamin D and parathyroid hormone levels. Similarly, zinc supplementation can increase appetite, but takes a long time to work and has be chronically given as a supplement for a long period of time, but studies have not been statistically significant. Ghrelin is an endogenous ligand for growth hormone secretagogue receptor that is produced by gastric endocrine cells which stimulates appetite, food intake and increases lean body mass. The downfall of ghrelin is that is has a short half-life and is only given in the parenteral form so therefore, it is not recommended for use.[1, 7]

Mirtazapine

Mirtazapine is a noradrenergic and serotonergic antidepressant which leads to effects of increased appetite, sedation, mood regulation, gastric mobility and increased body weight. It is used off label for increase appetite and body weight at doses ranging from 15-30mg by mouth once a day for 4 weeks. The evidence from studies are mixed on if it actually improves appetite or not. There is an ongoing study titled "Effect of Mirtazpine vs Placebo in Reversing Anorexia in Non-Small Cell Lung Cancer" that is assessing the use of mirtazapine and we need more conclusive evidence before it can be completely recommended; however, it does have a more favorable side effect profile compared to other agents.[1]

Nutrition

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines defines inadequate nutritional intake as a patient who cannot eat more than a week or if the estimated energy intake is <60% of requirement for 1-2 weeks. The guidelines recommend that cancer associated malnutrition should be treated with nutrition counseling, physical therapy, potential artificial nutrition and drug therapy in severely malnourished patients. They also recommend a whole person approach using nonpharmacologic treatment as well. [8]

Clinical Application and Expert Opinion

In my experience with cancer patients, it is best to offer counseling to not only the patient, but the family and caretakers. It is always best to try to prevent it by proper patient education than when it actually happens. It is also best to work with a nutritionist to help with a nutritional plan that takes the patients' lifestyle and treatment plan into consideration. There is a great deal of controversy on if we should even use appetite stimulating agents at all in cancer patients and research is ongoing. ●●

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Board Update

A Future-Forward Approach

Jolynn Sessions, PharmD, BCOP, FHOPA
HOPA President (2024-2025)
Oncology Pharmacy Manager, Charles George VA Medical Center
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As a new year approaches, I want to reflect on everything HOPA volunteers, staff, and leaders have accomplished. I also want to look ahead – and not just to the next calendar year (though that is important too and previewed briefly below.) The future I'm talking about is the forecast for associations in the next few years.

Future Foresights are Here

The HOPA Board recently worked with the American Society of Association Executives (ASAE) Research Foundation to take a deep dive into the top 50 Drivers of Change we need to address now and in the not-too-distant-future.

If you're thinking about AI, work automation, and evolving information channels, you are on the right track. But there is also digital currency, a multi-generational workforce, a new Presidential Administration (and according to ASAE, *so much more*, to consider!)

We will share more about HOPA's Future Forward initiatives and open up opportunities for members to engage in planning and innovating as this work continues. If you want to delve into the technological, social, regulatory, and demographic challenges – *and opportunities* – that lie ahead, please watch for these announcements.

Much Has Been Accomplished in 2024

Practice Management learning was reimagined. Our first single-topic, live, virtual practice management session took place in November, with more scheduled for each quarter of 2025. The most recent session, "Operationalizing Bispecific Therapies: From Engaging T-cells to Care Teams" had nearly 100 live attendees and we anticipate more learners will earn the 1.5 ACPE credit hours when it is released on-demand this month.

TIL therapy education provided for oncology pharmacists and nurses. We recently partnered with Oncology Nursing Society (ONS) for TIL therapy webinars. The three-part series explored the implementation and adoption for TILs therapy in various cancer care settings. Two of the three sessions offered CE credits and are now available in HOPA Learn; the first session is also available on our YouTube channel.

Time to Talk Diversity in Clinical Trials has launched. Thanks to industry support from BeiGene, Daiichi-Sankyo, Regeneron, and Eisai, we recently launched a new initiative to help increase the representation of Black, Indigenous, and People of Color (BIPOC) patients in cancer clinical trials. Check out Time to Talk Diversity in Clinical Trials on our website to access resources for your practice and your patients, including the history of cancer clinical trials, clinical trial myth busters, and more.

HOPA's DEI efforts have had an impact. The HOPA Diversity, Equity, and Inclusion Advisory Group has outlined steps our association has taken to make our operations, educational programs, and events more inclusive and welcoming. Tactics include updated nominations criteria to ensure fairness and transparency and enhancements to content and programming for better accessibility. We anticipate a recap to be released in January of 2025.

Improvements have been made to JHOP. HOPA has collaborated with Amplity Health, the publisher of the Journal of Hematology/Oncology Pharmacy, to increase readership, accessibility, and impact through marketing efforts, indexing, and online visibility. HOPA now has editorial control and independence over content, the peer-review processes, and editorial policies to help maintain the journal's integrity and alignment with the HOPA's mission.

HOPA 2025 is April 9-12 in Portland!

If you haven't already, please save the dates of April 9-12, 2025, for HOPA's Annual Conference in Portland, Oregon. In addition to the great science, sharing, and networking of our conference, the event promises outstanding scenery and a chance to experience some of the vibe that makes Portland, Portland. Early bird registration will open this month – we hope you can join us!

HOPA
Hematology/Oncology
Pharmacy Association

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HOPA 2025

Together we can reach new heights

We are hard at work to make your HOPA 2025 experience complete!

Come for the cutting-edge science and industry-leading presenters and stay for plenty of HOPA networking and events.

Plus, use your complimentary transit pass to get out and explore Portland!

We look forward to seeing you at HOPA 2025!

April 9-12, 2025 in Portland, Oregon at the Oregon Convention Center.

Early bird registration opens mid-December 2024! *Watch for details on hoparx.org.*

ABOUT THE HOPA 2025 VENUE:

- Open spaces and natural light set the scene for meaningful meet-ups with colleagues and friends!
- The **Oregon Convention Center's** commitment to sustainability sets HOPA up for our "greenest" conference to date
- The venue is a short walk or quick MAX Light Rail ride away from the hotel