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GBEMTI Perspectives – U.S. Managed Care Perspectives on Assessment and Uptake of Molecular Diagnostics: State of the Union and Areas for Additional Improvement

Eric Faulkner, Joshua Ransom, Geneva Briggs, PharmD, John Hanna

Summary
Payers view molecular diagnostic testing as high-impact to improving health outcomes and controlling health care costs, but there remain barriers to successful uptake. Compared with a previous survey of medical directors conducted by the GBEMTI, medical director understanding of clinical utility as related to molecular diagnostics has improved. Key challenges in the assessment and uptake of molecular diagnostics (including companion tests used in personalized medicine applications) covered in this paper include (a) inconsistent application of evidence requirements in the evaluation of molecular diagnostic tests (including across various test applications such as prediction, screening, diagnosis, treatment selection, and monitoring), (b) limited understanding of the validation and trial design considerations for molecular diagnostics, (c) inconsistency in the application of the definition of clinical utility, (d) lack of transparency and uniformity in weighting the factors that are utilized to determinate medical policy coverage for molecular diagnostics. In addition, other factors were highlighted in the survey but have been covered elsewhere, such as (e) complex coding environments make it difficult to link test types/brands/manufacturers to outcomes and costs and (f) payment policies do not reflect the value diagnostics bring to health decision making and patient care.

Payers (or their third party HTA vendors) ideally need to focus their technology assessment processes in a more standardized fashion on evaluating the role of the test in addressing a particular clinical scenario in a manner that is transparent to test providers and that ideally will assess the full episode of care to which the diagnostic will have an impact. This GBEMTI Perspectives paper considers the current “state of the union” for test evaluation in U.S. managed care, taking feedback directly from both payers and test providers, and discusses areas for improving the future state of molecular diagnostic HTA assessments and uptake.

Introduction
Molecular medicine has been revolutionizing health care for more than a quarter century, ranging from recognition of the role of cell surface markers as therapeutic targets to complex application of our growing knowledge of molecular networks and systems biology. Molecular diagnostics that link patient factors to appropriate treatments have also ushered in a new era of personalized medicine that approaches patient management at the individual level. The “next generation” of tests beginning to emerge now that promise to more holistically evaluate molecular interactions and disease root cause hold the potential to further reconfigure the health care landscape in half this time.

Some have called molecular diagnostics the $5 billion conundrum and others have referred to them as a tsunami overtaking health care. The worldwide market value of MDx by 2017 is estimated at $8.1 billion, though in reality this is but a tiny fraction of the overall $6.5 trillion worldwide health care tab. It has been well established that diagnostic testing influences over 70 percent of health care decisions, leading us to believe that molecular diagnostic spend is inherently providing significant value in high cost disease areas such as cancer treatment.
Today, the NIH Genetic Testing Registry (GTR) lists over 14,000 different gene-specific tests commercially available in a broad range of clinical indications. Payers know that these new molecular tests can be valuable, but have trouble evaluating them, have inconsistent evidence expectations, are concerned about the budget impact, and historically have had difficulty quantifying their ultimate benefit to patients due to ambiguous coding.

In order to gain a better understanding of the issues surrounding the assessment and uptake of molecular diagnostics (MDx), a targeted Internet-based survey was conducted by the Genomics, Bio-tech, and Emerging Medical Technologies Institute (GBEMTI) of the National Association of Managed Care Physicians (NAMCP) member medical directors. Additionally, conversations with members of the Executive Leadership Council (ELC) of the GBEMTI were held to gain additional perspective.

**Methods**

The GBEMTI was established in 2011 as an institute of the NAMCP. The NAMCP represents medical directors from payer, purchaser (employers), and provider systems such as independent practice associations (IPAs), accountable care organizations (ACOs), physician-hospital organizations (PHOs) and medical groups. The goal of the GBEMTI is to support and characterize the value of genomics, biotechnology, regenerative medicines and medical technologies as these new modalities enter and impact the health care system. The GBEMTI seeks to support collaborative stakeholder engagement around emerging health technologies to consider their potential to improve patient outcomes, impact on managed care management practices and value to the health care market place. The GBEMTI is unique in that it is a multi-stakeholder group centered on bringing medical director decision makers and manufacturers together to address key trends and topics that are transforming U.S. health care and explore means to improve managed care decision making and patient access to emerging health technologies.

To address the objectives of the Institute, divisions in the GBEMTI are each focusing on developing a series of perspective papers. The goal of this series of papers is to evaluate payer/managed care perspectives and implications for improving managed care processes, policies, and patient outcomes for each core emerging technology area. Personalized medicine and molecular/genomic diagnostics was selected as a key emerging technology topic with significant impact potential on managed care medicine. This paper and all subsequent ones published by the Institute have been peer reviewed by the GBEMTI ELC.

The survey questions addressed key drivers, information needs, and payer perspectives on opportunities for moving towards integration of MDx. The
survey was randomly disseminated to medical director members of the NAMCP and 56 total responses were obtained, 41 of which included complete surveys. Of the total respondents, approximately 70 percent identified themselves as medical directors at commercial managed care organizations (MCOs), and 30 percent identified themselves as medical directors of health system and provider organizations (e.g., academic medical centers, hospital and other health systems, large physician practices). The sample also included payer decision makers from leading U.S. MCOs (i.e., Aetna, Cigna, WellPoint, United Healthcare), which collectively represent more than 115 million covered lives in the U.S. Additional feedback was obtained through multiple working sections of the GBEMTI ELC.

Limitations of this analysis may include respondent bias, as it was not possible to determine whether respondents held a particular interest in personalized medicine and diagnostics and/or are early adopters. Based on the limited number of respondents, survey findings may not be fully representative of U.S. medical director perspectives, but do point to trends in payer and provider views on medical devices.

Perceived Impact of Personalized Medicine and Molecular Diagnostics

When asked about the impact of emerging new technologies, over 60 percent of respondents viewed the impact of personalized medicine and companion diagnostics on managed care as high to very high impact on balancing quality and cost (Exhibit 1). This is in contrast to other emerging areas such as nanotechnology where only 40 percent viewed the impact on quality and cost as high or very high. This is likely due to few current demonstration technologies available in the clinic. Other technology areas anticipated to have a significant impact on balancing quality and cost include medical devices, vaccines, and biologicals.

Evaluation of Molecular Diagnostics

According to this survey, 56 percent of plans do not have established criteria specific to the evaluation/coverage of MDx (Exhibit 2). Of those plans with established criteria specific to MDx, over 50 percent mentioned limited understanding of issues surrounding diagnostic evidence development, indicating that significant education requirements remain as personalized medicines and MDx increasingly enter managed care practice. It appears that management of molecular diagnostics appears to be increasing in focus, but is not yet a uniform priority among commercial plans in comparison to past NAMCP member research.

Of those health plans with established criteria, approximately 60 percent indicate using a standard framework developed by external third party or advisory organizations (Exhibit 3). The most commonly identified criteria used for assessment were ACCE, DNA Direct, and Interqual.8-10 Other approaches for assessment of molecular diagnostic evidence include BlueCross BlueShield Technology Evaluation Center (BCBS TEC), Evaluation of Genomic Applications in Practice and Prevention (EGAPP), Center for Medical Technology Policy (CMTP), and Institute of Medicine (IOM) that have advanced a range of concepts and standards for health technology assessment (HTA).11-14 However, these approaches are far ranging, none have been adopted as a central standard, and some do not appreciate practical issues associated with the imbalance
between evidence expectations and system incentives for MDx value recognition.

A significant percentage of health plans (almost 20%) outsource their evaluations (Exhibit 3). Based on ELC feedback, this is a growing trend for mid-sized and smaller health plans that lack the resource staff and economies of scale to maintain a robust HTA process that can keep pace with the wide variety of technology development. When technology assessment is outsourced, the process and criteria for HTA can be opaque to consumers, academics and biotechnology industry stakeholders and the assessment may be conducted without input from experts with specific domain knowledge such as pertinent physician specialty societies.

Standards for molecular diagnostic test evaluation were viewed as less clear, and more subjective and dependent on the particular clinical scenario than other technology types. Respondents stated that plans employ varying requirements across tests to establish medical necessity or clinical utility because no single accepted standard or approach has emerged. Few plans require prior authorization for MDx in addition to where a companion diagnostic is part of the prior authorization criteria for a particular drug. Test evidence viewed as “unclear” often resulted in designation as experimental/investigational. The most common reasons for this cited in ELC discussions are that tests lack a clear linkage between test use and changes in clinical decision making in the “real world”.

Respondents also indicated a tendency to lump
diagnostics into a general assessment category, consistent with our finding that less than half have specific criteria for MDx, even though the test application/use and value proposition may be significantly different. This approach may not take into account that different test applications (e.g., risk assessment, screening, diagnosis, treatment selection, and monitoring) all of which may have different attendant evidence questions/considerations and suggests that education on linking test application to HTA standards remains a key gap.

Demonstrating the impact of molecular testing on the improvement of patient health outcomes was also noted as important, but some payers acknowledged that direct studies of MDx conducted in a drug-like, randomized, controlled manner, outside of drug/MDx co-development which almost always involve randomized controlled trial (RCT) designs, may not be feasible in practice.15-17 The acceptable study type for stand-alone MDx, without predicate comparators, was generally viewed as a well-controlled observational cohort study, ideally with a comparator arm such as historical controls. Methodological specifics beyond this were not addressed although others have covered this in more detail.

If in fact well-controlled observational studies were deemed adequate to demonstrate these outcomes, why are not more tests covered that have this level of evidence? The answer may be that conventional HTA evolved with a primary emphasis on treatment assessment (which addresses different evidence questions than diagnostics) and involves use of evidence hierarchies "statically" without linking methods to evidence questions appropriately. Acceptance among the payer community of alternate study endpoints (e.g., changing physician decision making as a proxy for health outcome) and/or study designs (e.g., retrospective-prospective hybrids) will be a necessary prerequisite in order to allow more rapid adoption of these technologies for the benefit of patients. Indeed we have seen evidence emerge in other surveys of medical technologies for the benefit of patients. Indeed we have seen evidence emerge in other surveys of medical

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Factors cited as inhibiting development of robust diagnostic criteria included limited understanding of MDx issues, lack of standards, and the fact that MDx has not yet become a sufficiently significant priority compared with other health care reform and management priorities and that specific MDx criteria are not necessary (Exhibit 4). Over half of the respondents indicated that they have not initiated criteria due to limited understanding of MDx vocabulary and decision issues. Almost 35 percent indicated that specific criteria were either not a priority or not necessary yet. More appropriately, however, respondents indicated that there does need to be more appropriate definitions, study endpoints, and agreement between payers and test developers as to when molecular tests meet the existing standards of (1) changing physician decision making, (2) improving health outcomes and (3) defining standards for sufficiently stringent performance.

Movement towards more standard processes may more easily enable payers to apply a consistent framework to assess these technologies and improve consistency of coverage and reimbursement decisions. Commercial payers in ELC discussions acknowledged that RCT designs are not generally seen in practice or necessary in many cases—but did indicate that greater clarity around acceptable study standards for diagnostics would be welcome. Many ELC member payers were open to alternate study designs, so long as key questions about test impact on physician decision making and/or patient management were appropriately addressed, and at least indirectly linked to outcomes. This represents an educational opportunity for both test providers and HTA thought leaders.

Payer Perspectives on the Value of Diagnostics

Participants in the GBEMTI survey were asked to define clinical utility as it relates to MDx. Around half of payer respondents correctly defined clinical utility by the textbook definition of “the test being used to improve outcomes” and this number rises to almost 80 percent when “change to patient management” is included, given that change in management is logically linked to an assumption of improved outcomes (and may be established by linking evidence bridging patient management to outcomes).19-21 This is a significant increase from our 2009 NAMCP publication, which found that only 38 percent could correctly define clinical utility.15 This improvement suggests that stakeholder familiarity with diagnostic terminology and issues is increasing steadily as new technologies enter the market. Some have posited that the definition of clinical utility may change depending on diagnostic application.22 Approximately 23 percent of payer respondents incorrectly defined clinical utility as test performance alone, reflecting lack of familiarity with diagnostic terminology and need for education by industry and other stakeholders. This suggests that that variable interpretation of terminology such as clinical utility and application to decision practices remains a key confounder to consistent patient access decisions for diagnostics.

When asked about the test-value evidence consid-
Considered to be most important to informing reimbursement policies, there was no clear majority in the responses (Exhibit 5). The leading factors identified were test use informs change in patient management/care pathway and clinical utility, representing approximately 45 percent of the responses. Other factors such as test application, test performance, and cost-effectiveness (defined loosely as value for money in the U.S. context) were also noted as important, but considered as secondary. From the survey, respondents that correctly defined clinical utility appeared to be about twice as likely to view clinical utility or a change in patient management as most important compared to those that defined clinical utility incorrectly. More importantly, health plans that prioritized “clinical utility” and “demonstrated changes to patient management” were almost twice as likely to have correctly defined clinical utility (p<0.01). This suggests that standardization and education efforts could lead to a greater payer prioritization of clinical utility and identifies a key payer segment for targeting such efforts (Exhibit 6).

Consistently, clinical utility, test application, and impact on care pathway were also the most commonly cited drivers of coverage policy setting (Exhibit 7). A variety of other factors such as test performance, test cost and cost-effectiveness were considered, though these were proportionally less...
important to coverage decision making for a majority of respondents.

It is important to note that absolute test performance is relative to the clinical scenario – i.e., that tradeoffs between sensitivity and specificity are appropriate given intended use of the test and that no test will be fully both sensitive and specific. While payers seek the highest possible test performance, some payers acknowledged that incremental improvement to patient management and outcomes were better indicators of value. Additionally, test provider ELC members suggested that some tests may fill an unmet need by improving certainty of decision making where no objective alternatives exist. In such cases, comparison of absolute test performance versus current standard of care (e.g., as defined in practice guidelines or established historical controls) may better clarify improvements in care pathways influenced by diagnostics, even perhaps if performance of the innovator test is moderate.

Evidence cited as being most frequently absent from reimbursement submissions to payers from this survey included (a) “test use informs a change in patient management/care pathway” (38.7%), (b) “cost-effectiveness against standard of care tests” (35.5%), (c) “incremental test performance (improvement over other tests for the same marker)” (22.6%), and (d) “clinical utility” (22.6%). This aligns with previous analyses of HTA on MDx tests which found these same factors as frequent drivers of negative coverage policy decisions for diagnostics. Payer respondents confirmed that “test use resulting in change in patient management” has been infrequently demonstrated in standalone diagnostics studies to date, with some notable exceptions like Oncotype Dx for breast cancer. In addition, emphasis on addressing this key question appears to be increasing significantly in recent years for tests such as C-Methionine PET testing in brain tumors.

While most payers seek information on the clinical utility of a test, demonstration of clinical utility in practice has been historically difficult for test developers – in large part because of the “moving target” of this definition among real-world decision makers. While most stakeholders agree that test performance data (sensitivity, specificity, and predictive value) is foundational for diagnostic reimbursement, it is not sufficient, in and of itself, for value demonstration. The scope and nature of evidence to practically demonstrate clinical utility has been heavily debated, with some postulating that clinical utility may vary by test application.

ELC payer members indicated that that demon-
strating a test changes patient management and is an appropriate surrogate for “improving patient outcomes” in the context of managed care decision making – at least in cases where the relationship between the management change and outcome improvements are supported by a sufficient evidence base. However, when presented with such information, some payers may withhold coverage, stating that the test developer must demonstrate improvement in longer term patient outcomes. This finding also underscores the variability in understanding of diagnostics evidence development among the managed care community and the need for improved consistency in diagnostics HTA and coverage decision making. Overall however, ELC payer members were very open to (a) clarifying diagnostic evidence standards – noted as a key gap and area of difficulty/confusion and (b) better understanding rationale supporting a reasonable evidence package in this technology area that balances real-world challenges in evidence development with the payer’s need to assess a sufficiently robust evidence-base to support coverage determinations.

Conclusions and Key Gaps to Address in Diagnostic Value Demonstration
As molecular diagnostics continue to enter the marketplace and influence health decision making, payer uncertainty around technology appraisal of these technologies remains, though a majority of surveyed plans have begun to develop criteria for evaluation. As science and information technology evolve faster than highly-regulated, resource-constrained health systems can integrate the changes, establishing a transparent and consistent base for evaluation and coverage of diagnostics will be critical to appropriate uptake and value realization. Of the factors discussed, the following are key areas for additional focus:

- **Establishing a clear and consistent understanding around diagnostic terminology** so that stakeholders communicate clearly and effectively. The complex and heterogeneous language currently existing around diagnostics (e.g., nuances among terms like genetics and genomics) continue to impede value discussions and policy formation. For example, variable interpretation of clinical utility’s definition remains a confounder to consistent evaluation of diagnostic value and may also influence uptake as financially-at-risk provider models expand.

- **Clarifying evidentiary expectations, including study designs for diagnostics.** Many ELC members understood that these diagnostic evidentiary issues are different compared to therapeutics technologies, but lack consistent perspective on “what good looks like” for tests, including by test application. ELC members were also very open to an actionable reference of diagnostics-specific study considerations to help guide test HTA. These expectations would of course need to be aligned with appropriate market incentives for evidence development.

- **Developing clarity around complex test evaluation**, for example, involving dozens to thousands of biomarkers that will likely have algorithmic or interpretive components. Many ELC members were concerned that the industry is advancing panels/complex tests that include biomarkers whose value is unknown and expressed apprehension around paying for test information that is unnecessary or may be harmful to patients. The ELC did anticipate that as tests advance that the cost per biomarker may drop significantly and the value of diagnostic information will increase substantially.

- **Integrating feedback from test developers into the technology assessment process to provide appropriate context on the clinical situation and ensure informed assessment.** While network clinicians have routinely provided such input to medical policy decisions, the pace of technology development may require that medical directors seek this additional input.

- **Initiating a consistent format and expectations for diagnostic value communication**, including a dossier template that managed care decision makers can leverage to support reimbursement evaluations was cited as a key need. The NAMCP has helped to facilitate this by working with the GBEMTI ELC and test providers to develop and roll out such a format in the near future that will be publically available to all stakeholders.

- To help realize the potential of leveraging diagnostic information to improve care, clarifying scenarios or instances where targeted diagnostic pilots may help better define episodes of care or novel applications.

While some of the above factors have been discussed for some time in diagnostic and personalized medicine “circles,” all have bearing on improving the consistency and appropriateness of managed care decision making around diagnostics. Ultimately, our results show that understanding and evaluation of molecular diagnostics is improving among the managed care medical director community we surveyed. Medical directors believe that personalized medicine and molecular diagnostics will have a significant impact on health care quality and costs. While the majority of plans have not developed medical policy criteria specific to molecular tests, most are using standard frame-
works, such as AACE, to help make informed policy decisions. In order to help managed care organizations adapt to emerging technologies and innovation, future research efforts will need to consider other areas not included in this paper, such as broader health system integration considerations, “big data” challenges of leveraging diagnostic data, issues around “next generation” testing (i.e., complex panel tests, algorithmic tests, and broader genomic or systems biology information) that may stimulate refinement of best practices in molecular medicine. As we continue to move into an era where our ability to produce diagnostic information rapidly outstrips the ability of health systems and policies to keep pace, addressing these more fundamental considerations would lay a solid foundation for current and near-term managed care.

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References


PROSTATE CANCER IS THE NUMBER ONE cancer in men by incidence and is projected to remain first. After initial definitive treatment, many men will develop recurrent or advanced cancer which will eventually become castrate-resistant prostate cancer (CRPC). CRPC is defined as disease progression despite androgen deprivation therapy (ADT) and castrate levels of testosterone (< 20ng/dL). It presents as a spectrum of disease ranging from increasing PSA levels without metastases or symptoms and despite ADT, to metastases and significant debilitation from cancer symptoms (metastatic CRPC, mCRPC). Once the state of androgen independency occurs, historically the median overall survival was only eight to 16 months from the time of its appearance. Currently, for patients with CRPC, the median progression-free survival ranges from 12 to 30 months once treatment is initiated. CRPC does not necessarily imply hormonal resistance altogether. There is a molecular basis underlying retained hormone sensitivity in CRPC. Amplification of the androgen receptor locus (AR) occurs in approximately 30 percent of CRPC tumors, but not in tumors prior to therapy. There is enhanced intracellular conversion of adrenal androgens to testosterone and dihydrotestosterone in the cancer cells, intratumoral androgen synthesis, increased expression of AR messenger RNA, and ligand-independent AR activation.

The AR remains active in most patients with CRPC. Guidelines from the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO) and others recommend that ADT be continued in patients with CRPC. Historically, ADT was continued until documented mCRPC then the patient received chemotherapy. This was poorly tolerated with low response rates and minimal clinical benefits prior to 1991. In the 1990s, the role of chemotherapy was re-evaluated with development of better-tolerated regimens that improved quality of life and overall survival (OS). In 2004, docetaxel was approved for first-line treatment of mCRPC. Cabazitaxel (Jevtana®) in combi-
nation with prednisone was approved in 2010 for use in mCRPC previously treated with docetaxel.

Docetaxel binds and stabilizes tubulin, induces cell cycle arrest, and inhibits cell proliferation. Two pivotal studies using docetaxel in combination with prednisone and estramustine in one trial showed an improvement in median OS of 2.4 months and 0.9 months compared with mitoxantrone, the previous first-line chemotherapy.\(^8,9\)

Cabazitaxel was approved based on a trial comparing it in combination with prednisone to mitoxantrone plus prednisone. The median OS was 15.1 months in the cabazitaxel group versus 12.7 months with mitoxantrone (HR 0.70; 95% CI 0.59–0.83; \(P<0.0001\)).\(^10\)

Sipuleucel-T (Provenge\(^8\)), an immunotherapy FDA approved in 2010, is recommended as first-line treatment for asymptomatic or minimally symptomatic metastatic CRPC.\(^6\) A course of sipuleucel-T treatment consists of three basic steps. A patient’s white blood cells, primarily antigen-presenting cells (APCs), are extracted in a leukapheresis procedure. The blood product is incubated with a fusion protein (PA2024) consisting of two parts, the antigen prostatic acid phosphatase (PAP), which is present in 95 percent of prostate cancer cells, and immune signaling granulocyte-macrophage colony-stimulating factor (GM-CSF) that helps the APCs to mature. The activated blood product (APC8015) is returned to the infusion center and infused into the patient to cause an immune response against cancer cells carrying the PAP antigen. A complete sipuleucel-T treatment repeats three courses, with two weeks between successive courses. The cost is about $31,000 per infusion and $93,000 for a complete treatment. Acute infusion reaction is the most common adverse effect and was reported in 71.2 percent of clinical trial patients. Patients are premedicated with oral acetaminophen and an antihistamine to prevent the reaction. Sipuleucel-T provides a median of a 4.1 month survival benefit over placebo.\(^11\)

Other treatment options after sipuleucel-T and chemotherapy focus on targeting androgen production and the androgen receptor. Two agents – abiraterone (Zytiga\(^8\)) and enzalutamide (Xtandi\(^8\)) – target the androgen receptor in different ways and have been FDA approved.

Abiraterone is a CYP17 modulator that inhibits steroidogenesis. CYP17 is essential for biosynthesis of androgens and adrenal hormones and implicated in aberrant intratumoral androgen production. This agent provides more potent and durable androgen suppression than ketoconazole, another CYP17 inhibitor.\(^12\) It blocks two critical steps in testosterone biosynthesis – conversion of pregnenolone to 17 OH-pregnenolone and conversion of 17 OH-pregnenolone to dehydroepiandrosterenedione. This agent is effective even in patients resistant to ketoconazole.

The FDA approved abiraterone in 2011 for patients with progression after docetaxel. In late 2012, the FDA expanded approval to treat men with mCRPC prior to receiving chemotherapy. The cost of this agent is approximately $18,000 for 12 weeks of therapy.

Because of the adrenal metabolic pathways altered by this agent, it must be given with daily prednisone. Adrenal insufficiency can occur if daily steroid dosing is interrupted, or during times of infection or stress. Other common adverse effects with abiraterone include fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, anemia, hypercholesterolemia, hyperglycemia, increased liver function tests, hyperphosphatemia, and hypokalemia. The most commonly observed difference between CRPC cells and hormone-sensitive prostate cancer cells is AR overexpression. Enzalutamide is a second-generation AR antagonist with no agonist activity in the setting of androgen receptor over expression. It has high affinity binding to the AR-ligand binding domain with inhibitory activity. Enzalutamide was FDA approved in 2012 for patients with mCRPC with prior docetaxel treatment. Over time, this agent will be used earlier in therapy because it is a better androgen blocker than the currently used agents; it acts through three different pathways within a cancer cell to block the effects of testosterone. This agent costs $7,450 per month, wholesale.

Compared with placebo in a randomized, double-blind study in mCRPC patients previously treated with at least two chemotherapy agents, enzalutamide resulted in a 4.8 month difference in median OS.\(^13\) Median OS was 18.4 months in the enzalutamide group and 13.6 months in the placebo group. At the time of prespecified interim analysis, enzalutamide use resulted in a 37 percent reduction in risk of death as compared with placebo (HR for death, 0.63; 95% CI, 0.53 to 0.75; \(P<0.001\)). The OS benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region and type of disease progression at entry. Enzalutamide was also better than placebo for all the secondary endpoints – prostate-specific antigen (PSA) level response rate, soft-tissue response rate, quality of life, time to PSA progression, radiographic progression-free survival, and time to first skeletal-related event.

Enzalutamide does have significant potential for serious drug-drug interactions. Strong CYP2C8 inhibitors need to be avoided and so do CYP3A4,
CYP2C9 and CYP2C19 substrates with narrow therapeutic index. The reported adverse effects of this agent include asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, muscular weakness, dizziness, insomnia, hematuria, paresthesia, anxiety, increased blood pressure, and seizures.

Another aspect of caring for patients with CPRC is preventing skeletal-related events (SREs) secondary to bone metastases. More than 90 percent of patients with mCRPC develop bone metastases and decreased bone integrity. SREs include fracture, bone pain, and spinal cord compression, which significantly impacts quality of life. Additionally, bone loss is associated with ADT, which further increases risk of fracture. To prevent SREs, all patients on ADT should get vitamin D and calcium supplementation.

In addition to vitamin D and calcium, the NCCN guidelines recommend specific therapy to preserve bone health and to prevent SREs in patients with bone metastases. Zoledronic acid (Zometa®, a bisphosphonate given intravenously every three to four weeks, is recommended in men with CRPC and bone metastases to prevent SREs. Denosumab (Xgeva®) is a RANK ligand inhibitor given subcaneously every four weeks. Both have been shown to decrease SREs. The NCCN guidelines recommend denosumab as an alternative to zoledronic acid for prevention of SREs.

Zoledronic acid is not recommended if the patient’s baseline kidney function is less than 30ml/min. Good oral hygiene, baseline dental evaluation for high-risk patients, and avoidance of invasive dental surgery during bisphosphonate therapy is recommended to reduce risk of osteonecrosis of the jaw.

Exhibit 1 compares zoledronic acid and denosumab. In a cost-effectiveness analysis from a U.S. payer perspective, denosumab resulted in fewer estimated SREs (-0.241; 1036 vs 1.277), more QALYs (0.0074; 0.9306 vs 0.9232), and lower SRE-related costs (-$2,340; $4,424 vs $11,164) than zoledronic acid. Those benefits came at a higher drug-related cost ($10.181; $23,144 vs $12,963) and higher total costs ($7,841; $31,968 vs $24,127).

Bone pain is a significant effect of mCRPC. Strontium 89 (SR-89) is a targeted option for treating pain related to bone metastases. It is close to calcium in the periodic table and is a beta-emitter that has a higher affinity for tumor containing bone than normal bone. Its half-life in normal bone is considerably shorter than in tumor containing bone (14 versus 50 days). The most frequently observed toxicities are associated with bone marrow suppression of 11 to 65 percent in more than 50 percent of patients. Blood counts return to normal within eight weeks after treatment and rarely does severe toxicity occur when given to patients with normal hematological parameters.

Radium-223 (Xofigo®, formerly Alpharadin) is another option for treating bone metastases. It was granted fast-track designation by the FDA in May 2013 for treating patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. Radium-223 is an alpha-particle-emitting radionuclide that mimics calcium and is incorporated in osteoblastic bone lesions. It delivers short range, high energy which minimizes myelotoxicity. This is the first bone-targeted therapy to show an effect on OS; Radium-223 increased OS by 3.6 months compared to placebo. Significant OS benefit was demonstrated in both a chemotherapy-naive and a post-docetaxel group. It also extends median time to first SREs (15.6 vs 9.8 mos). The most common nonhematologic adverse effects include diar-
rhea, nausea, vomiting and constipation. Neutro-
penia occurred in 4 percent of study subjects and
thrombocytopenia in 8 percent.

The current management of CRPC is outlined in
Exhibit 2.17 There are numerous agents which pro-
vide incremental increases in survival but there are
unanswered questions of how best to use the vari-
ous therapies. Optimal sequencing of the approved
agents, duration of use of each agent, how to com-
bine agents to maximize survival and minimize
toxicity, and which patients will benefit the most
(or the least) are questions to be answered.

Prospective data addressing optimal treatment se-
quencing are not available and head-to-head com-
parisons of new therapies (i.e., abiraterone versus
enzalutamide) are not available. Pre-clinical data
suggest that use of additional treatments may allow
expansion of prostate cancer clones with mutations
conferring resistance to subsequent therapies.18,19 For
example, prior abiraterone treatment appears to ad-
versely impact docetaxel activity in small studies;
further data are needed to determine best sequential
use of docetaxel. Studies combining docetaxel with
other agents generally demonstrate increased toxic-
ity and equal or inferior survival when compared to
standard regimen.

For sequencing abiraterone, there are no direct
comparisons of first versus second-line abiraterone.
Extrapolating from pre- and post-docetaxel studies,
abiraterone appears to have higher rates of PSA de-
cline and soft tissue responses when administered to
chemotherapy-naive patients. When used as third-
line therapy, the activity of abiraterone appears to
be reduced after exposure to both enzalutamide and

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**Exhibit 2: Current Management of mCRPC**

<table>
<thead>
<tr>
<th>Metastatic, asymptomatic, chemotherapy-naive</th>
<th>Metastatic, symptomatic, chemotherapy-naive</th>
<th>Metastatic, post-docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>Docetaxel</td>
<td>Abiraterone, Enzalutamide</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>Abiraterone</td>
<td>Cabazitaxel, Mitoxantrone</td>
</tr>
</tbody>
</table>

**Bone-directed therapy**
- Zoledronic acid, denosumab for all bone metastases
- Samarium for symptomatic bone metastases
- Radium-223 prolongs survival

**Prostate cancer treatment continuum**

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**Exhibit 3: Principles for Drug Development for Men with mCRPC**

- Optimize drug delivery and minimize unnecessary harms and costs to individuals and society by developing predictive biomarkers for the new systemic therapies.
- Prevent, not just delay, death from prostate cancer by studying the early use of effective systematic therapies prior to macrometastatic disease.
- Improve our preclinical models and human correlative studies to better understand the molecular underpinnings of how prostate cancer metastasizes, resists current therapies, and changes over time.
- Develop screening strategies and biomarkers that ID men with aggressive, potentially lethal organ-confined PCA but don’t detect the indolent nonlethal disease.
- Ensure the real clinical value of therapies by developing transparent guidelines that account for society-level values.
docetaxel. A variety of studies are ongoing evaluating combination therapy with abiraterone.

Only limited data are available evaluating sequential administration of enzalutamide after abiraterone and docetaxel. Enzalutamide appears to have higher activity in docetaxel-naïve patients. For third-line therapy after prior docetaxel and abiraterone, one retrospective cohort analysis of 35 patients demonstrated that complete cross-resistance was not observed and 3/19 (16%) who had not responded to abiraterone achieved PSA declines of greater than 50 percent on enzalutamide. 20

Cabazitaxel is typically used after docetaxel failure, but there are concerns regarding third-line cabazitaxel; clinical data suggest that both docetaxel and abiraterone may target the AR signaling pathway to reduce activity. Currently, no prospective data address this. Retrospective cohort data suggest that cabazitaxel retains significant activity when used in third-line setting.

Exhibit 3 lists some proposed principles for new agent development for treating prostate cancer which can help address some of the unanswered questions regarding optimal treatment. 21

**Conclusion**

Several new agents have been approved for the management of CRPC with unique mechanisms of action and indications. Patients with CRPC will ultimately require multiple agents over time as their disease evolves. Currently, new therapies are used in patients with metastatic disease, but there may be a role for them earlier in the course of the disease. The timing of use of each of these therapies in metastatic disease is not well defined and the efficacy of therapy may be affected by prior therapy.

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**References**

THE INCIDENCE OF MELANOMA HAS INCREASED dramatically since the 1930s (Exhibit 1). About one in 60 Caucasian Americans will be diagnosed with melanoma in their lifetime. According to the American Cancer Society, an estimated 9,480 people in the United States died from advanced melanoma in 2013. Many patients will develop metastatic disease, which is considered incurable. The treatment of metastatic melanoma includes chemotherapy, oncogenic pathway inhibitors, and immunotherapy. Because of the low response rates, chemotherapy is now reserved as a last line of therapy. In addition to these treatments, the National Comprehensive Cancer Network (NCCN) guidelines include clinical trials as a preferred therapy.

Targeted therapy has changed how melanoma is treated. These agents target oncogenic pathways of growth including BRAF. Vemurafenib (Zelboraf®) was the first FDA approved targeted therapy for melanoma. It was approved in 2011 for metastatic melanoma in patients who had a tumor with BRAF V600E mutation. The name “vemurafenib” comes from V600E mutated BRAF. The overall response rate in a trial comparing vemurafenib to dacarbazine was 48.4 percent versus 5.5 percent, respectively. The adverse effects of this agent are arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous cell carcinoma, photosensitivity, nausea, and diarrhea. Approximately 15 to 30 percent of melanoma patients treated with BRAF inhibitors develop cutaneous squamous cell carcinomas and keratoacanthomas within the first few weeks of therapy, but the mechanisms underlying the rapid formation of these secondary malignancies remain incompletely characterized but may be related to paradoxical activation of certain pathways in cells with oncogenic mutations. In the preapproval trial, 38 percent of patients required dose modification because of adverse effects. Dabrafenib (Tafinlar®), another BRAF inhibitor, was FDA approved in 2013 for unresectable BRAF V600E/K melanoma. In the trial comparing dabrafenib to dacarbazine, there was an overall response rate of 50 percent versus 7 percent. The major dif-
ference between the two BRAF inhibitors is dabrafenib has some activity in the central nervous system. In one trial, nine of 10 patients with melanoma brain metastases had reductions in brain lesion size. The adverse effects are similar with the two BRAF inhibitors. This agent is also being investigated in other BRAF-mutated cancers. In 28 patients with BRAF-mutant nonmelanoma solid tumors, antitumor activity was noted in gastrointestinal stromal tumors (GISTs), papillary thyroid cancer, non-small cell lung cancer NSCLC, ovarian cancer and colorectal cancer.

If only a single tumor growth pathway such as BRAF is blocked, the cancer can use other growth pathways to continue to grow. Blocking mitogen-activated protein kinase (MEK) alone and in addition to BRAF is being investigated. Trametinib (Mekinist®) is a MEK inhibitor FDA approved in 2013 for unresectable BRAF V600E/K melanoma. Again, compared with dacarbazine, the response rates were higher with trametinib (22% vs 8%). Importantly, there is little to no clinical activity in patients who had previously progressed on BRAF inhibitors; therefore, this agent is not a treatment option for resistant tumors. This agent commonly causes rash (80%) and diarrhea (~40%). Peripheral edema, cardiomyopathy, interstitial lung disease, and retinal vein occlusion and retinopathy can also occur.

In January 2014, the FDA approved the combination of trametinib and dabrafenib for unresectable or metastatic V600E/K melanoma. Approval was based on demonstration of durable response rate and improvements in disease-related symptoms, but improvement in overall survival has not yet been shown for the combination. In a trial of 162 patients randomized to the combination compared with dabrafenib monotherapy, there was a higher response rate with the combination based on investigator evaluation but not a difference in independently assessed duration of response (Exhibit 2). Regulators in Europe have not approved the combination. Interestingly, the incidence of squamous cell carcinoma is lower when a MEK inhibitor and BRAF inhibitor are used together.

Targeted therapy often works quickly and effectively, which is good for patients who need an immediate response. Unfortunately, responses are not durable; resistance often develops after six to eight months. Essentially, targeted therapy is used as a bridge to reduce disease burden before starting immunotherapy.

Melanoma is perhaps the most immunogenic human cancer, and the immune system can be trained to attack the disease. The human immune system can attack with virtually unlimited precision. The immune system can adapt to ongoing tumor mutations and avoid drug resistance, thus immunotherapy responses are often durable because of immune memory. Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself.

Interleukin 2 was the first immunotherapy approved for melanoma. This is an intense therapy that has to be administered in an ICU; approximately 100 centers in the U.S. currently give this therapy. It yields a 15 to 20 percent response rate with 5 percent of those being long-term responders. The adverse effects are major and include hypotension, tachycardia, capillary leak syndrome, and altered mental status. Interleukin 2 can only be used in relatively healthy, young patients with no brain metastases. Receiving IL-2 does not preclude the patient from getting another therapy. The opposite is not always
true because of the long-term adverse effects of the other therapies.

Ipilimumab (Yervoy®) blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), an immune checkpoint molecule that down-regulates pathways of T cell activation. It was FDA-approved for the treatment of metastatic melanoma after a 676-patient, randomized study demonstrated improved overall survival (44% versus 25% at one year). This agent is given intravenously as four doses over nine weeks. If someone responds to ipilimumab, they can have a durable response (i.e., years).

Because ipilimumab blocks CTLA-4, the immune system does not have a good braking system so it can become overactive. Serious autoimmune-related adverse events occur in 20 percent of patients, with a 2 percent mortality rate seen in a premarketing study. These serious events include immune-related colitis, hepatitis, toxic epidermal necrosis, hypophysitis, and nephritis.

Management for most of the immune-related adverse effects is based on severity. In general, grade 1 to 2 adverse effects are treated with supportive care and possible withholding of ipilimumab. With grade 3 to 4, corticosteroids and discontinuation of ipilimumab are required. For example, with severe enterocolitis, the ipilimumab would be permanently discontinued and systemic corticosteroids would be started; infliximab can be used if the colitis is refractory to corticosteroids.

Anti-programmed cell death 1 (PD-1) monoclonal antibodies are another area of immunotherapy. PD-1 is a protein on the surface of activated T cells. If another molecule, called programmed cell death 1 ligand 1 (PD-L1), binds to PD-1, the T cell dies or has reduced activity. This is a way that the body regulates the immune system, to avoid an overreaction. Since many cancer cells make PD-L1, the cancer cells can disarm the T cells and inhibit them from attacking the tumor. Pembrolizumab and nivolumab are two anti-PD-1 agents that blocks PD-L1 from binding to PD-1.

Pembrolizumab (Keytruda®, formerly lambrolizumab) was approved by the FDA on September 4, 2014 as a breakthrough therapy for use following treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in patients who carry a BRAF mutation. It binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including antitumor immune response. In one trial in patients with ipilimumab-resistant disease, a 26 percent response rate was seen.

Nivolumab is another anti-PD-1 agent still under investigation. In Phase 1 trials, it has been well-tolerated in patients with treatment-resistant cancers; tumor regressions were seen in patients with melanoma, kidney, colon, and lung cancer. In a study of nivolumab in advanced melanoma after multiple systemic therapies, the median overall survival was 16.8 months. The one-year survival rate was 62 percent and the two-year survival rate was 43 percent. Seventy-one percent of patients who discontinued therapy for reasons other than disease progression maintained responses off-therapy for at least 16 weeks (range, 16 to 56+ weeks). One example of response was in a 71-year-old man with colorectal cancer who had disease progression after surgery and chemotherapy. A partial response was seen after one dose of nivolumab, and he received four more doses over six months, resulting in complete response. A complete response has been maintained for five years off therapy.

Blockade of the PD-1 immune checkpoint pathway can induce durable antitumor responses that can persist even after discontinuation of therapy, which is distinct from chemotherapy and oncogenic

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**Exhibit 2: Dabrafenib and Trametinib**

<table>
<thead>
<tr>
<th></th>
<th>Overall Response Rate (%)</th>
<th>Complete Response (%)</th>
<th>Median Duration of Response (mos)</th>
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<tr>
<td>Investigator Assessment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>D + T</td>
<td>76</td>
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<td>10.5</td>
</tr>
<tr>
<td>D alone</td>
<td>54</td>
<td>4</td>
<td>5.6</td>
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<tr>
<td>Independent Radiology Review Committee Assessment</td>
<td>D + T</td>
<td>57</td>
<td>9</td>
</tr>
<tr>
<td>D alone</td>
<td>46</td>
<td>7</td>
<td>7.6</td>
</tr>
</tbody>
</table>
pathway inhibitors (e.g., BRAF inhibitors). This suggests a shift in equilibrium between tumor and host and supports the use of checkpoint blockade therapies early in the course of treatment in appropriate patients.

After immunotherapy, a patient’s tumors will appear to grow when measured on a CT scan and then begin to shrink and even disappear. The early growth changes on CT scan are likely pseudo-progression that is an immune reaction occurring. Response patterns to checkpoint blockade therapies, including anti-PD-1, are unique, necessitating the development of new technologies that can distinguish immune cell activity from tumor growth.14

Re-induction can also be done with immunotherapy. As an example, a 55-year-old woman with metastatic melanoma had a mixed response after one dose of nivolumab. She had a partial response after additional doses and maintained response for 16 months off therapy. She then developed new thoracic adenopathy, which was confirmed to be melanoma by biopsy. Re-induction with nivolumab led to a partial response for 21 months. She then received ipilimumab and had a stabilization of her disease.14

Re-induction therapy with anti-PD-1 can reset the equilibrium between the tumor and the host’s immune system, re-establishing immune-based control of tumor growth. This raises the as yet unanswered questions of whether maintenance therapy is needed to preserve equilibrium or if there is a way to detect recurrences very early so the patient could get a booster dose.

The combination of ipilimumab and anti-PD-1 therapies is under study.15 Although effective, this is a fairly toxic combination with greater than 50 percent of patients having a grade 3 or 4 immune-related adverse effect.

Conclusion
There has been a shift in the treatment paradigm for melanoma. Immunotherapy, rather than chemotherapy, has become first line. The preferred therapies for metastatic melanoma are immunotherapy, targeted therapy for disease burden reduction, and clinical trials.

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References
MULTIPLE MYELOMA (MM) IS A CANCER of the plasma cell characterized by excessive numbers of abnormal plasma cells in the bone marrow. Many improvements in treatment have occurred over the past 14 years (Exhibit 1). With the introduction of novel agents and stem cell transplants, the outcome for patients with MM has improved in recent years, both in the relapsed setting as well as at diagnosis. Once considered relapsed or refractory, the disease is considered incurable, and the goal of therapy changes to disease stabilization and symptom minimization.

Relapsed disease is the first progression in the absence of any therapy. It can be a biochemical or symptomatic relapse. Relapsed and refractory disease is progression on specific therapy or within 60 days of completion of a given therapy. Dual refractory disease is resistant to bortezomib and lenalidomide. Primary refractory disease is defined as no response following initial induction therapy.

Once someone relapses after initial induction therapy, they are committed to remaining on therapy for the remainder of their life; median survival in the relapsed/refractory setting is six to nine months. Relapsed/refractory MM can be treated with multiple lines of treatment, including retreatment with a previous agent, but the response declines with each subsequent treatment (Exhibit 2). Many factors have to be considered in choosing treatment at relapse (Exhibit 3).

Novel agents for MM include immunomodulators [thalidomide (Thalomid®), lenalidomide (Revlimid®), and pomalidomide (Pomalyst®)] and proteasome inhibitors [bortezomib (Velcade®) and carfilzomib (Kyprolis®)]. Other treatment options include chemotherapy, novel agents in combination with chemotherapy combinations, salvage autologous stem cell transplant, allogeneic stem cell transplant, and clinical trials.

Carfilzomib and pomalidomide are the most re-
Recently approved agents. Carfilzomib, a selective irreversible proteasome inhibitor, has been studied in relapsed/refractory MM. Given intravenously, it resulted in a 23.7 percent overall response rate in a heavily pretreated population.\(^1\) The response lasts a median of 3.7 months, with overall survival of 15.6 months. The most commonly reported adverse effects with carfilzomib are thrombocytopenia and anemia. The major distinction from bortezomib, a reversible proteasome inhibitor, is a lower rate of peripheral neuropathy.

Pomalidomide, an immunomodulatory lenalidomide analogue, was FDA approved for relapsed/refractory MM in early 2013. When studied in a heavily pretreated population, 31 percent of patients achieved an overall response rate with pomalidomide in combination with dexamethasone.\(^2\) Progression-free survival was four months compared with 1.9 months for dexamethasone alone. Overall survival was also longer with the combination (12.7 vs 8.1 months). Like lenalidomide, cytopenias are the most frequent adverse effects of this agent. Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on therapy or within 60 days of completion of the last therapy.

The combination of pomalidomide and carfilzomib has been studied in relapsed/refractory MM.\(^3\) The majority of subjects in this study were refractory to lenalidomide and bortezomib. Combination therapy resulted in a significantly higher response rate (70%) than seen with either agent alone.

More than 300 agents are under study for MM with some of the most promising agents listed in Exhibit 4. Ixazomib is the agent closest to market and is the first oral proteasome inhibitor. Phase I/II studies using ixazomib weekly or twice weekly in relapsed/refractory MM patients suggested antitumor activity of the single agent, but more promising results have been obtained with the combination of ixazomib, lenalidomide, and dexamethasone in newly diagnosed MM.\(^4\)

Oprozomib (ONX-0912) is a structural analog of carfilzomib that is also an oral agent. This proteasome inhibitor binds selectively and irreversibly to its target. Different formulations of this agent are under investigation. A 20 percent overall response
rate was seen in a Phase Ib/II dose escalation study in heavily pretreated MM. 5

Panobinostat, another oral agent, is a nonselective histone deacetylase inhibitor (HDAC inhibitor) being investigated in many different cancers. It increases acetylation of proteins involved in multiple oncogenic pathways. Combination with a proteasome inhibitor results in a buildup of intracellular misfolded cytotoxic proteins, leading to MM cell apoptosis through synergistic inhibition of the aggresome and proteasome pathways. 6 The combination of bortezomib and panobinostat appears to be effective in those with bortezomib resistance (31% overall response rate).

Monoclonal antibodies against myeloma-specific antigens are also under investigation and appear to

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**Exhibit 2: Best Response to Regimen, by Regimen Number**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CR%</th>
<th>VGPR%</th>
<th>PR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>35</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2nd</td>
<td>30</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>3rd</td>
<td>25</td>
<td>5</td>
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</tr>
<tr>
<td>4th</td>
<td>20</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5th</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Exhibit 3: Factors in Selecting Treatment for Relapsed/Refractory Myeloma**

1. **Disease-related factors**
   - Duration of response to initial therapy
   - FISH or cytogenetic profile (e.g., t(4;14) or p53 deletion)

2. **Regimen-related**
   - Prior drug exposure (relapsed vs refractory)
   - Toxicity of regimen (combination vs single agent)
   - Mode of administration (oral, SQ vs IV)
   - Previous transplant (durability of response after transplant)

3. **Patient-related factors**
   - Pre-existing toxicities (e.g., cumulative myelosuppression, peripheral neuropathy)
   - Co-morbid conditions (e.g., renal failure, diabetes mellitus)
   - Age
   - Performance status
   - Distance from Center
   - Insurance
have significant activity.8 Daratumumab, a fully human IgG1k monoclonal antibody that targets CD38, has demonstrated promising activity as monotherapy and in combination with other novel agents in patients with relapsed/refractory multiple myeloma, resulting in the initiation of several Phase III clinical trials. Elotuzumab is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein. CS1 is highly and uniformly expressed on MM cells while there is restricted expression on NK cells and little to no expression on normal tissues. Preliminary results from a trial in combination with lenalidomide-dexamethasone showed an overall response rate of 82 percent in a relapsed/refractory population.

Conclusion

Many treatment options are available for patients with MM that has relapsed. When selecting salvage therapy, numerous factors including disease-related, patient-related, regimen-related, and prior therapy have to be considered. Although strides have been made in improving survival, better agents are still needed. Numerous agents, which will hopefully make it to market, are under study.

Christina Gasparetto, MD is an Associate Professor of Medicine at Duke University Medical Center.

References


### Exhibit 4: Promising Novel Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixazomib (MLN9708)</td>
<td>Proteasome inhibitors</td>
</tr>
<tr>
<td>Oprozomib (ONX-0912)</td>
<td>Proteasome inhibitors</td>
</tr>
<tr>
<td>Marizomib (NPI-0052)</td>
<td>Proteasome inhibitors</td>
</tr>
<tr>
<td>Rocitinostat (ACY-1215)</td>
<td>HDAC inhibitors</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>HDAC inhibitors</td>
</tr>
<tr>
<td>Filanesib (ARRY-520)</td>
<td>Kinesin Spindle Protein</td>
</tr>
<tr>
<td>Afuresertib (GSK2110183)</td>
<td>AKT inhibitor</td>
</tr>
</tbody>
</table>

HDAC = histone deacetylase
AKT = protein kinase B
IN 2013, THERE WERE 228,190 NEW CASES OF lung cancer diagnosed in the United States.¹ Lung cancer caused 160,000 deaths in 2013, which is comparable to deaths from prostate, pancreas, breast, and colon cancer combined.¹ The annual rates of lung cancer, unlike other cancers, had been increasing with a peak around 1990 and have since been declining.² Smoking among women was the main contributor to the rate increase. Annually, twice the number of women die from lung cancer compared to breast cancer.

Smoking is the main cause of lung cancer in the U.S. Only 10 to 15 percent of cases are in never smokers. In never smokers, second-hand smoke exposure; occupational exposure to asbestos, arsenic, and chromium; domestic radon; and environmental pollution all contribute to lung cancer cases. Environmental pollution, which comes from transportation, stationary power generation, industrial and agricultural emissions, and residential heating and cooking, is increasingly recognized as a carcinogen.

There have only been very minor improvements in survival in lung cancer. About 15 years ago, the five-year survival rate was 13 percent, which has only increased to 17 percent currently. More than 50 percent of those affected by lung cancer have disease beyond the lung at diagnosis. Close to 40 percent of cases are advanced (Stage IV) disease at presentation.

A decade ago, the primary treatment for advanced non-small cell lung cancer (NSCLC) was chemotherapy. The combination of a platinum-based agent with other chemotherapy was the standard of care and produced a modest improvement in overall survival. Therapy has changed since then based on three main discoveries.

The first discovery was that response to certain agents varied based on tumor histology. In a trial comparing pemetrexed/cisplatin to gemcitabine/
cisplatin, squamous cell disease responded better to gemcitabine. Those with nonsquamous disease had a better overall survival with pemetrexed. The theoretical reason that nonsquamous disease responds better is that pemetrexed inhibits thymidylate synthase in cancer cells and the expression of this synthase is much higher in squamous, so the medication is not as effective. Prior to this, all NSCLC subtypes were viewed together and treated the same.

A second important discovery that changed the way lung cancer is treated was the development of bevacizumab, an angiogenesis inhibitor. An important aspect of any cancer is its ability to induce development of new blood vessels, so it can grow and metastasize. Bevacizumab inhibits vascular endothelial growth factor (VEGF), which plays a key role in the regulation of angiogenesis. In combination with standard chemotherapy in nonsquamous cell lung cancer, a significantly higher percentage of patients in the bevacizumab group were alive at 12 months (51% vs 44.4%) and 24 months (22% vs 15.4%). The median overall survival was 12.3 months versus 10.3 months for the bevacizumab plus chemotherapy compared with chemotherapy alone. In preclinical trials with bevacizumab, it was found that patients with squamous cell tumors had a much higher likelihood of hemoptysis, thus these patients should not receive this agent. Although modest benefit was shown with bevacizumab, this was the first and only agent to show survival benefit when given with a platinum-based combination regimen. Other three-agent regimens have not shown survival benefit.

The third discovery that has changed the treatment paradigm from platinum-based chemotherapy for everyone with advanced NSCLC is the identification of molecular drivers of cancer growth and therapies targeted against these drivers. If the drivers of tumor growth can be identified and blocked, tumors can be effectively treated. One of these drivers in lung cancer is endothelial growth factor receptor (EGFR). In about 10 percent of NSCLC tumors, the EGFR gene is mutated such that the EGFR receptor is constantly active, leading to increased cell survival, growth, and metastases. EGFR mutations occur more commonly in tumors in never or very light smokers and in adenocarcinoma. In adenocarcinoma, the mutation occurs in 17 percent of cases.

Studies have shown that erlotinib (Tarceva®), which inhibits EGFR, improves disease control and duration of control compared to chemotherapy. The NCCN guidelines recommend EGFR mutation testing of nonsquamous cell tumors. If positive, an EGFR inhibitor is indicated for treatment. It is important to note that even with EGFR inhibition, the cancer will usually progress via the development of alternative pathways of growth and additional genetic mutations for cell clones within the tumor. Continuation of EGFR inhibitors is recommended even when progression occurs because some parts of the tumor will continue to be controlled by the medication. Trials are ongoing examining response to additional agents which can target more mutations in cases of secondary progression.

When secondary progression occurs, the personalized treatment approach requires identifying the mutations driving tumor growth in a given individual and then selecting therapy to target those factors. Identification of the mutations driving secondary progression requires a re-biopsy of the tumor.
Another tumor mutation, echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (EML4–ALK), drives tumor growth in about 5 percent of patients. A small inversion within chromosome 2p in NSCLC cells results in the formation of a fusion gene comprising portions of EML4 and ALK. ALK positive NSCLC is more common in younger patients with adenocarcinoma and in never smokers. Testing for this mutation has also become standard of care.

Within four years of identification of this mutation, a targeted therapy, crizotinib (Xalkori®), was approved. Crizotinib is an ALK inhibitor that is active in ALK-rearranged NSCLC. Dramatic tumor reductions are seen in patients with advanced EML4–ALK-positive NSCLC with crizotinib treatment. In the main trial of this agent, 54 percent of patients were still alive at two years and the median overall survival had not been reached when the trial was published. Eventually, the cancer will develop resistance for which many mechanisms have been identified. Selective, second-generation ALK inhibitors to overcome resistance are under study.

One exciting aspect of these new targeted therapies is their effectiveness in the brain. Historically, the blood brain barrier limited the ability to treat brain metastases. Surgery and radiation had to be used. There is limited delivery of targeted therapy, but it is enough to have a clinical effect.

Many other mutations are under investigation and will become part of standard testing (Exhibit 1). The genetic drivers of growth can be identified in 60 percent of tumors completely tested. Given all that has been discovered about NSCLC, the catch-all term NSCLC really should be abandoned and replaced with each individual subtype name such as adenocarcinoma and that tumor’s specific mutations. The majority of genetic drivers have been identified in adenocarcinoma, but there are data to show that even in squamous cell disease mutations can be identified.

Other therapies are on the horizon. Immunotherapy is now in the experimental testing stage for NSCLC. Cancer cells have mutations that make them recognizable by the immune system. However, cancer cells can evade immune surveillance by T cells by expressing proteins such as programmed death ligand (PD-L1). Inhibiting the PD-L1 from interacting with its receptor (PD-1) can restore antitumor T cell activity, potentially leading to long-lasting responses. There is preliminary evidence of activity with PD-1 or PD-L1 agents.

Immunotherapy is not a cancer therapy per se; it allows the immune system to overcome the blockade by the cancer. Although only about 20 percent of patients respond to immunotherapy, if they respond, the response tends to be long lasting (a year or more). Tumor PD-L1 expression may be one of the markers developed to identify those who would likely respond. There are a great deal of immune checkpoints which can be targeted and different cancers may use different checkpoints to evade the
immune system. Science is just in the beginning stages with these.

Identifying lung cancer earlier is another way to improve survival. Lung cancer is definitely a disease which benefits from screening. In people with a 30-pack a year smoking history, low-dose CT has been shown to reduce the risk of death from lung cancer by 20 percent, and there was an increase in overall survival by 7 percent compared with a screening chest x-ray (Exhibit 2). This is the first screening test to show an effect on overall survival. The U.S. Preventive Services Task Force recommends that asymptomatic adults between 55 and 80 with a 30-pack a year smoking history and still smoke or quit within the last 15 years be screened annually with low-dose CT.

Conclusion
In reality, a disease called non-small cell lung cancer is no longer treated. This disease should be categorized based on underlying histology and molecular drivers because this is how treatment is selected. Testing for various targets has become an integral part of management of NSCLC with multiplex testing coming. This is the beginning of personalized therapy.

Shirish M. Gadgeel, MD is the Leader of the Multidisciplinary Thoracic Oncology Team at the Karmanos Cancer Institute at Wayne State University in Detroit, MI.

References
8. Kris MG. The Lung Cancer Mutation Consortium. Presented at: 12th Annual Targeted Therapies in Lung Cancer; February 2012; Santa Monica, CA.
PULMONARY HYPERTENSION (PH) IS EL-evated pressure within the pulmonary vascular bed which can have many causes (Exhibit 1).1 Pulmonary arterial hypertension (PAH) is one type of PH which has increased pulmonary vascular resistance (PVR) as a consequence of structural changes to the pulmonary arteries. The pulmonary pressures by right heart catheterization which classify someone as having this condition are an increased mean pulmonary arterial pressure (mPAP, $\geq$ 25 mm Hg), a normal pulmonary capillary pressure, and increased PVR.

The symptoms of PAH develop and progress as the ability of the heart to maintain or increase cardiac output is compromised and the right ventricle progressively fails. The initial signs and symptoms include dyspnea (on exertion), fatigue, pre-syncpe, edema, dizziness, and angina. The nonspecific nature of these complaints can lead to confusion with other conditions and a significant delay in establishing the diagnosis. Also patients can present at various points during the progression of this condition. Most people do not seek care until the symptoms truly bother them. As demonstrated in the case in Exhibit 2, it can take a year or longer to get an appropriate diagnosis. Typically it takes 1.5 years for diagnosis.

Ultimately, PAH results in right heart failure and death. Although there are treatments for PAH, it has the highest mortality rate of all the forms of PH. To properly treat PAH, the cause and severity must be known.2 The evaluation of someone suspected of having PAH will include a review of a patient’s history, a physical, laboratory tests, a chest x-ray, an electrocardiogram, and pulmonary function tests. Evaluation may also include a ventilation-perfusion lung scan, a pulmonary angiography, an echocardiogram (at rest, and/or with exercise), an exercise test (including an assessment for arterial oxygen desaturation during exertion), a sleep study, and right heart catheterization.

The primary goals of therapy are to prevent clinical worsening, reduce symptoms, and to improve hemodynamics, quality of life, exercise capacity, daily function, and survival. Treatment is both symptomatic and targeted to underlying pathophysiology of PAH. General medical management of PAH includes oxygen which may be required at rest, with exertion and/or at night, warfarin (for certain types of PAH), diuretics, and digoxin (if right ventricle dilated and/or depressed). Supportive therapies include supervised exercise programs, with avoidance of strenuous exercise. Numerous lifestyle adjustments are also necessary. Those with PAH need to avoid stimulants and decongestants that contribute to vasoconstriction. They should be on a low-salt diet and may need fluid restriction. Additionally,
avoidance of pregnancy in women is recommended. Women with PAH who try to carry a pregnancy to term have a 30 percent chance of dying.

The small percentage of patients who have a positive vasodilator response on testing will be treated with a calcium channel blocker with vasodilatory properties such as nifedipine or amlodipine. These medications are much less expensive than the agents used in those who do not have vasodilator response. It is essential to follow patients treated with calcium channel blockers closely to make sure the clinical response is as anticipated, to make sure there are no side effects of therapy, and very importantly, to make sure the response is sustained.

Many altered pathways and mediators have been identified that contribute to the cell proliferation and

---

**Exhibit 1: Clinical Classification of Pulmonary Hypertension**

1. PAH
   - Idiopathic PAH
   - Heritable
   - Drug and toxin-induced
   - Persistent PH of newborn
   - Associated with:
     - CTD
     - HIV infection
     - Portal hypertension
     - CHD
     - Schistosomiasis
   - PVOD and PCH

2. PH Owing to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular Disease

3. PH Owing to Lung Disease and/or Hypoxia
   - COPD
   - ILD
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypventilation disorders
   - Chronic exposure to high altitude

4. Chronic Thromboembolic PH

5. PH with Unclear Multifactorial Mechanisms
   - Hematologic disorders/splenectomy
   - Systemic disorders
   - Metabolic disorders
   - Others

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**Exhibit 2: Example Case**

- A 40 year-old woman seen in emergency department for an episode of syncope after running up two flights of stairs.
- She had been seen by PCP one month prior for dyspnea x five months. She is unable to walk up hills in neighborhood, unable to lift her 5 year-old daughter without dyspnea/lightheadedness.
- History of childhood asthma
- Diagnosed by PCP with asthma; PFTs = mild restriction
- Examination/Testing
  - Exam unremarkable except for HR 110/min and trace pedal edema
  - Brain CT unremarkable
  - Neuro evaluation negative
  - No CP, wheezing, orthopnea, PND, leg pain or swelling
- Referred to pulmonary clinic
- FEV1 normal, slightly reduced FEF 25 - 75%, O2 sat 0.99%
- ABG: pH 7.45  pO2 93   pCO2 33
- Thus, unexplained dyspnea, syncope with exercise and unexplained tachycardia
- Still with tentative diagnosis of asthma
- Three months later, seen in ED for worsening dyspnea
  - Concern for cardiac cause; echo with RVSP 70mm Hg
  - Referred to Pulmonary Hypertension clinic
- After further testing (including right heart cateterization), finally receives PAH diagnosis one year after symptoms started
Vasoconstriction in PAH, which ultimately ends in vascular remodeling. Targets of current PAH specific therapies include the prostacyclin, endothelin, and nitric oxide pathways. Endothelin constricts pulmonary arteries and is blocked, whereas endothelin and nitric oxide are vasodilators. Targeting each of these pathways results in vasodilation and antiproliferative effects in the pulmonary vasculature. The FDA approved therapies for PAH by class include: endothelin receptor antagonists - oral bosentan (Tracleer®), oral ambrisentan (Letairis®), oral macitentan (Opsumit®); prostacyclin analogues - continuous IV infusion epoprostenol (Flolan®, generic), continuous IV infusion thermostable epoprostenol (Veleti®), continuous SC or IV infusion treprostinil (Remodulin®), inhaled iloprost (Ventavis®), inhaled treprostinil (Tyvaso®); phosphodiesterase type 5 inhibitors - oral or IV sildenafil (Revatio®, generic), oral tadalafil (Adcirca®); soluble guanylate cyclase stimulators – oral riociguat (Adempas®)

Selection of initial PAH specific medication will depend on the severity of symptoms, rate of progression, evidence of right-heart failure, 6-minute walk distance, and brain natriuretic peptide levels. The dosage form selected will also depend on the capability of the patient to manage inhaled or parenteral therapy. Parenteral therapy is first choice therapy in rapidly progressing and advanced disease. Other issues to consider include drug-drug interactions, adverse events, comorbid conditions (e.g., diabetes), dosing, and cost. Exhibit 3 outlines which classes of agents are used based on severity. Typically one agent is started and then the patient may be switched to another agent. The use of combination therapy is more common than in the past and is being evaluated in multiple ongoing studies.

A wide range of therapeutic options are in clinical research for PAH. Additionally, prospective controlled trials of combination therapy with currently or soon-to-be approved agents are ongoing. In the future, other therapeutic approaches may provide additional benefits to patients with this life-threatening disease.

**Conclusion**

The diagnosis of PAH can be elusive; often the diagnosis is delayed for greater than one year after the onset of symptoms. Dyspnea on exertion is the most common symptom, but a careful exam will usually reveal clues to the diagnosis. Right heart catheterization is required for making the diagnosis. With more than ten agents now approved for PAH, inroads are being made in improving survival for this devastating disease.

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**References**


Type 2 diabetes mellitus (T2DM), which accounts for 95 percent of all cases of diabetes, is a disease of progressive beta cell failure. Major pathophysiologic defects that occur in this disease are qualitative and quantitative impaired b-cell function, decreased insulin sensitivity (insulin resistance), and glucagon excess. As the beta cell failure progresses, all medications, except insulin, will begin to fail, which results in increasing hemoglobin A1C (A1C, Exhibit 1).1 Because of their mechanism of action, most antidiabetic medications require some insulin secretory ability.

Current treatment goals are given in Exhibit 2.2-4 In general, the goal is to get A1C to 7% or below, but these goals are not being achieved.5 Around 50 percent of patients achieve appropriate A1C goals. Insulin use remains low in the United States, at approximately 20 percent of patients, despite high average A1C values.6 Interestingly, glucose control is poor even among insulin users. One study found insulin-treated patients had a mean A1C of 8.4%.7 In this study, 78 percent of the patients had an A1C over 7%, so 22 percent still don’t reach goal. There is significant resistance among clinicians to prescribe insulin because of the difficulty in initiating therapy and to appropriately escalate the insulin dose or regimen.

Diabetes control could be improved by better utilizing available medications. One of the newer classes are the GLP-1 receptor agonists. Incretins are released during nutrient absorption, augments insulin secretion at physiologic concentrations, and have glucose dependent insulinotropic effects. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are the two incretins that have been identified. These agents are secreted in response to eating and suppress glucagon secretion.8 Only GLP-1 agents have been developed. Those with type 2 DM have been shown to have suppressed GLP-1 secretion, resulting in lower post meal insulin secretion and higher postprandial glucose values compared to those without diabetes.9 GLP-1 receptor agonists, including liraglutide (Victoza®), exenatide (Byetta®), and albiglutide (Tanzeum®), are FDA approved for treating type 2 DM. These agents cause increased insulin secretion by increasing first-phase secretion, decreasing...
glucagon secretion, slowing gastric emptying, and increasing satiety to decrease food intake. These agents decrease A1C approximately 1%. Liraglutide and long-acting exenatide, both once-daily medications, reduce A1C more than twice-daily short-acting exenatide. Once a week formulations of exenatide (Bydureon®) and albiglutide are available for patient convenience.

The GLP-1 receptor antagonists have multiple nonglycemic effects, including improvements in beta cell function (in animals); reduction in food intake; renal, GI, and neuroprotective effects; and improvements in cardiovascular risk markers (lowering of weight, blood pressure, and lipids). Patients can lose a modest amount of weight (4 to 7 lbs) when started on a GLP-1 agonist.

The GLP-1 receptor antagonists have multiple roles in contemporary diabetes management. They can be used when target A1C is not being achieved, as monotherapy, as combination therapy, in two-drug combinations with metformin, in three-drug combinations, and in combination with basal insulin. Additional roles are when hypoglycemia is particularly undesirable, when weight gain is a concern, and to complement actions of other antihyperglycemic agents.

GLP-1 is rapidly metabolized by dipeptidyl peptidase 4 (DPP4) to inactive agents. The DPP4 inhibitors [sitagliptin (Januvia®), saxagliptin (Onglyza®), vildagliptin (Galvus®), linagliptin (Tradjenta®)] allow the GLP-1 naturally secreted to act longer. They are not as effective in lowering A1C as the GLP-1 agonists but are options for managing glucose.

At some point in the course of the disease, almost all patients will require insulin therapy to manage their disease. Exhibit 3 lists some considerations in initiating insulin. The indications for insulin use in T2DM are significant hyperglycemia at initial presentation and hyperglycemia despite diet, exercise and maximal doses of oral agents.

With initial presentation, insulin can be initiated
as two daily injections of a mix of intermediate and short-acting insulin, often 70/30 insulin. Metformin, unless specifically contraindicated, is very effective in addition to insulin. Insulin dose/type/number of injections are then adjusted as needed to reach target. As shown in Exhibit 4, starting insulin as initial therapy can result in long-lasting stable effects on A1C.17

Most patients end up on insulin after not reaching goal on several oral agents. There are many ways to initiate insulin, but a single bedtime injection of a long-acting insulin (glargine, detemir or NPH) at 0.4–0.7 units/kg/day is the typical first step. Insulin sensitizers, especially metformin, should be continued if there are no contraindications. GLP-1 agonists and DPP4 inhibitors can also be continued. Secretagogues (sulfonylureas) and α-glucosidase inhibitors should be discontinued to prevent hypoglycemia. Again the dose, type, and number of injections can be adjusted to achieve glycemic targets. Bedtime basal insulin is effective in helping patients who have failed oral therapy reach goal about 50 percent of the time.

When bedtime basal insulin therapy is not enough, therapy can be intensified using two or even three daily injections of premixed (70/30, 75/25) insulin. Two daily injections are more effective than bedtime insulin alone.18,19 The next step after two daily injections

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**Exhibit 3: Points to Consider when Implementing Insulin Therapy**

- Address patient concerns about insulin therapy
- Initial anxiety
  - Provide education and support
- Feelings of personal failure
  - Inform patient that type 2 diabetes is a progressive disease
- Fear of hypoglycemia
  - Education about signs and symptoms as well as prevention and treatment
- Fear of injections
  - Advise of availability of fine needles and injection devices
- Weight gain
  - Adjust diet and exercise as needed
- Communicate benefits of insulin therapy
- Insulin therapy is safe, effective and flexible; it can reduce the risk of diabetes complications and improve quality of life

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**Exhibit 4: Initial Insulin Treatment in Type 2 Diabetes**

<table>
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</tr>
</tbody>
</table>

HbA1c results %

-3 0 2 4 6 9 12 15 18 21 24 27 30 33 36 42
of long-acting insulin is to add premeal short-acting insulin before the largest meal. If that is not sufficient, another injection of premeal insulin is added before the second largest meal. When all else fails, premeal insulin before all meals is prescribed. Two injections of long-acting insulin and three premeal doses of short-acting insulin will get even more patients to target without a major increase in the rate of hypoglycemia. The downside of the five-injection regimen is patient difficulty with adherence. The last option is an insulin pump, but there is no major advantage over multiple daily injections for patients with T2DM.

A relatively new approach is to add a GLP-1 agonist to basal insulin or the reverse. This is an effective approach that minimizes the weight gain seen with insulin and the rate of hypoglycemia. The triple combination of insulin, a GLP-1 agonist, and metformin has also been shown to be effective.

**Conclusion**

Type 2 diabetes is a disease of progressive beta cell failure, which explains frequent and early oral therapy failure. After oral agent failure, injectable treatment with either GLP-1 agonists and/or insulin is indicated. GLP-1 receptor agonists have reasonable A1C lowering effects with low risk of hypoglycemia or weight gain. However, insulin treatment is usually inevitable and should be started sooner rather than later and treatment should be intensified as needed to meet A1C targets. Basal insulin is a simple, reasonable starting place, but basal insulin alone is successful only 50 percent of the time in achieving glycemic targets. Premixed insulin is a simple (for the patient and the health care provider) therapy and is effective in having patients achieve their targets 60 to 70 percent of the time. Multiple daily injection therapies and perhaps insulin pumps can be used when targets are not being achieved with less complicated regimens.

**References**

CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is characterized by airflow limitation that is not fully reversible and is progressive. There is an abnormal inflammatory response in the lung to particles or gases, but there are also significant extrapulmonary effects. The mechanisms underlying the airflow limitation are small airways disease with airway inflammation, airway fibrosis, luminal plugs, and increased airway resistance and parenchymal destruction with loss of alveolar attachments and decreased of elastic recoil.

Twenty-four million people are estimated to have COPD in the United States (Exhibit 1). The challenge with this disease is that about half of those remain undiagnosed. Part of the challenge of diagnosis is that COPD demographics are changing. Traditionally, this was perceived as a disease of elderly men, but women account for 60 percent of cases and 70 percent of those affected are younger than age 65.

The reason for the increase in women is that it became socially acceptable to smoke in the 1970s. Unfortunately for women, they are more susceptible to the effects of tobacco smoke. They get lung cancer at younger ages and lesser smoking history. The mortality from COPD in women is now higher than that of men.

COPD is the third leading cause of U.S. deaths. Exhibit 2 illustrates the rise in deaths by gender. Whereas the death rates from other major disease such as stroke and heart disease have declined, the death rates for COPD have risen significantly. This is primarily due to the increase in the number of people with COPD as a result of women entering the world of smokers.

In addition to the impact on mortality, COPD is an expensive disease. It results in 1.5 million emergency room visits, 726,000 hospital admissions, and 42 billion dollars of health care costs annually. More than half of those costs are a result of exacerbations.

In the U.S., 90 percent of the cases are caused by smoking. About 50 percent of lifelong smokers will get COPD. Other causes include work exposures, genetics (alpha-1 antitrypsin deficiency accounts for...
1% of cases), second-hand smoke, indoor and outdoor pollution, and recurrent childhood infections.

Typical symptoms of COPD are dyspnea on exertion, cough, and sputum production. These symptoms, particularly in someone with exposure to risk factors such as smoking, are suggestive of COPD and should prompt an evaluation; but, COPD cannot be diagnosed purely on clinical grounds. Spirometry has to be done to document airflow limitation and irreversibility. The values which define COPD are a forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of less than 70 percent and FEV1 is less than predicted. COPD is staged based on the severity of the airflow limitation (Exhibit 3).1

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines provide a structure for diagnosing and managing COPD. The goals of treatment are to relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations, prevent disease progression, and reduce mortality.

COPD disease management includes assessing and monitoring the disease, reducing risk factors, managing stable COPD with education, pharmacologic therapy, and non-pharmacologic therapy, and lastly, managing exacerbations. According to the GOLD guidelines, managing the disease is really more than monitoring the severity of the airflow limitation.1 Symptoms and frequency of exacerbations need to be assessed and monitored at each medical encounter.

Reducing risk factors requires reducing occupational exposures and environmental exposures, and smoking cessation. Reducing occupational exposures may require someone changing jobs. Patients need to be educated how to reduce their exposure to outdoor and indoor pollutants. Additionally, to prevent infections which complicate the disease, patients need influenza and pneumonia vaccinations.

Smoking cessation is vitally important for prevention of COPD and to slow progression in those who already have COPD. If patients stop smoking, even with severe disease, the progression is slowed significantly. All smokers should be assessed at each visit for willingness to initiate smoking cessation.

Patients need to be educated about their disease; many think that the diagnosis is a death sentence so treatment does not matter. The patient educational components include disease awareness, risk factor reduction, how and when to use medications, recognizing early symptoms of exacerbation, and need for healthy lifestyle including nutrition and exercise. Recognizing early symptoms of an exacerbation are particularly important in helping avoid hospitalizations.

COPD medications are either bronchodilators, corticosteroids, or phosphodiesterase 4 inhibitors. Bronchodilator medications are central to the symptomatic management of COPD. These are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms. Short-acting bronchodilators for as-needed use include short-acting beta agonists (SABAs), short-acting antimuscarinics (SAMAs), and combination products (SABAs/SAMAs). Long-acting agents include long-acting beta agonists (LABAs), long-acting antimuscarinics (LAMAs), and combinations of LABAs and inhaled corticosteroids. There is no role for inhaled corticosteroids alone in COPD. Oral corticosteroids are only indicated for treating an exacerbation and not for chronic therapy if at all possible.

The GOLD guidelines use a matrix approach that includes symptoms, severity, and risk of exacerbations for selecting initial therapy (Exhibit 4). Symptoms are assessed first using a symptom questionnaire. Next, the degree of airflow limitation using spirometry and history of exacerbations are determined. Two exacerbations or more within the last year or an FEV1 less than 50 percent of predicted
value are considered high risk. One or more hospitalizations for COPD exacerbations should also be considered high risk. Patients would be classified in one of four categories: A is fewer symptoms, low risk; B is more symptoms, low risk; C is fewer symptoms, high risk; and D is more symptoms, high risk.

Oxygen therapy is another component of non-pharmacologic therapy. Oxygen saturations should be checked in all patients. Blood gases should be checked if FEV₁ is less than 50 percent predicted and especially if oxygen saturation is less than 94 percent. Many patients have desaturation when exercising or during sleep and thus may need an exercise or nocturnal assessment. Indications for oxygen therapy include an oxygen pressure less than 55 or pressure between 55 and 59 with cor pulmonale, polycythemia, or cardiac disease. Patients should use oxygen at least 16 hours per day, which is the duration shown to reduce mortality.

Pulmonary rehabilitation is important but not widely available because of the lack of reimbursement. It significantly improves dyspnea, health-related quality of life, and walking distance and may decrease health care utilization and cost. Pulmonary rehabilitation is probably more important than pharmacotherapy.

Nutritional assessment is important in all COPD patients. Underweight patients with COPD have higher mortality than normal weight patients. Overweight patients have the additional comorbidities that come from excess weight.

Although AAT deficiency only accounts for 1 percent of COPD cases, the new GOLD guidelines recommend screening all COPD patients for the deficiency because specific treatment is available and it is not always easy to predict which patients have this genetic abnormality. High-risk patients include those with early onset (<45) disease, emphysema without risk factors, lower lobe bullous disease, and strong positive family history.

In addition to nutritional issues, other extrapulmonary effects of COPD include osteoporosis, depression, coronary artery disease, and cancer. The disease itself and the co-sharing of smoking each contribute to all of these except depression. Screening for each of these should be done in every COPD patient.

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<table>
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**Exhibit 3: GOLD Guidelines Severity Staging**

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<tr>
<td>3</td>
<td>30 - 49%</td>
<td>SEVERE</td>
</tr>
<tr>
<td>4</td>
<td>&lt; 30%</td>
<td>VERY SEVERE</td>
</tr>
</tbody>
</table>

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Exacerbations are common in COPD and, as mentioned earlier, account for more than 50 percent of disease costs. Seventy-seven percent of patients have at least one exacerbation per year. An exacerbation is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. Infection and air pollution are two common causes. The cause is unknown in one-third of cases.

Management of an exacerbation includes intensification of pharmacologic therapy with inhaled bronchodilators, oral corticosteroids, and antibiotics if signs of infection are present. Not every exacerbation requires antibiotics or oral corticosteroids. If patients have at least two symptoms of infection (increased sputum production, increased dyspnea, and sputum purulence), antibiotics are likely effective.

Preventing exacerbations can significantly reduce the overall costs of COPD management. Prevention is also important because frequent COPD exacerbations are associated with a higher rate of lung function decline and lower quality of life. Influenza and pneumonia can lead to exacerbations, so every patient needs an annual influenza vaccine and a pneumonia vaccine at appropriate intervals. Other therapies that have been shown to reduce exacerbation rates include ICS, LABA/ICS combination, tiotropium (Spiriva®, LAMA), and roflumilast (Daliresp®).

Roflumilast is a newer oral agent indicated for maintenance treatment of severe COPD in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment. It is a selective phosphodiesterase 4 inhibitor useful for preventing exacerbations. While the specific mechanism is not well defined, the therapeutic effect is thought to be related to the effects of increased intracellular cAMP in lung cells.

Combination of ICS/LABA can reduce the rate of exacerbations requiring hospitalization by 36 percent compared with a LABA alone. The number needed to treat for this combination is very favorable. Only two patients need to be treated with an ICS/LABA combination to prevent one exacerbation. Tiotropium reduces the risk of exacerbations and hospitalizations by 14 percent. Roflumilast reduces risk by 17 percent. These exacerbation prevention trials all included different types of patients, so comparative efficacy for the medications cannot be determined.

Another sometimes overlooked aspect of managing COPD is end of life planning. Unfortunately, advance directives are often not obtained, physician-patient communication is inadequate, and hospice is underutilized. Because COPD course is unpredictable, an end of life planning discussion should be initiated with all patients sooner, rather than later.
Conclusion
COPD is a leading cause of death in America; yet, it is underdiagnosed and undermanaged. The most recent GOLD guidelines use a matrix based on symptoms, severity, and exacerbations for determining appropriate therapy. Providers need to be educated on this revised approach.

Robert Sussman, MD is a Pulmonary Specialist at the Atlantic Health System Overlook Medical Center.

References
ATRIAL FIBRILLATION (AF) IS THE MOST common arrhythmia seen in clinical practice, affecting over three million Americans. Because of our aging population, it is estimated that it will affect 16 million by 2050. One in five strokes in the United States is the result of AF-related thromboembolism.

An individual’s risk of stroke can be estimated and is used for selecting therapy. CHADS₂ is a system for establishing the risk of stroke in patients with non-rheumatic AF.¹ Points are given for presence of heart failure, hypertension, age over 75, diabetes mellitus, and previous stroke or transient ischemic attack. CHA²DS₂VASc is a refinement of the older CHADS₂ score, which includes additional stroke risk factors and puts greater emphasis on age as a risk factor.² Exhibit 1 compares the two scoring systems. With either system, the risk of stroke increases with increasing score. Generally, they result in similar treatment recommendations. The newest update of the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines recommend the use of CHA²DS₂VASc for assessing stroke risk in nonrheumatic AF.³

Exhibit 2 outlines the recommended stroke prophylactic agents based on the CHA²DS₂VASc score.³ Antiplatelet therapy with aspirin is indicated in AF patients at low risk of stroke (score of 1). For those with higher risk (score of 2 or more), anticoagulation is recommended.

When taken appropriately, warfarin is effective in reducing stroke risk, but monitoring is required to ensure therapeutic range and many foods and medicines interact with warfarin. Despite efficacy, warfarin exposes patients to bleeding risks (e.g., intracranial hemorrhage and hemorrhagic stroke). Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans. Additionally, warfarin use represents a challenge to surgeries and there are high rates of discontinuation and nonadherence to therapy. Because of all these issues, warfarin is underprescribed in AF.⁴

Dabigatran (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®) are new anticoagulants FDA approved in recent years as alternatives to warfarin and are recommended by the recent guidelines. There have been single trials comparing each of the new agents with warfarin.

The RE-LY trial, a noninferiority trial, compared

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**Summary**

Because patients with atrial fibrillation (AF) are at significant risk for having a stroke, preventive therapy must be considered in every patient with AF. The choice of therapy will depend on the other risk factors for stroke, risk factors for bleeding present in the patient, and other concomitant conditions. New anticoagulants offer the promise of improved risk reduction with similar or lower risk of bleeding complications.

**Key Points**

- Stroke prophylaxis is important in patients with AF.
- New guidelines recommend using the CHA²DS₂VAS score for selecting therapy.
- If patients are well controlled on warfarin, they should stay on warfarin.
- Newer anticoagulants are alternatives to warfarin.
- An additional anticoagulant is close to FDA approval.
dabigatran and warfarin. This trial showed that dabigatran 150mg bid is superior to warfarin in low-to moderate-risk patients. The number needed to treat (NNT) for this trial was 150. Thus, 150 people would have to be treated with dabigatran before one patient efficacy over warfarin was achieved. In a subgroup analysis, dabigatran was only better than warfarin in patients who were poorly controlled on warfarin. Thus, efficacy benefit may not be seen in highly adherent warfarin-treated patients or in higher risk AF populations. If patients are well controlled on warfarin, they should stay on warfarin.

Adverse effects with warfarin and the newer anticoagulants are primarily bleeding issues. Dabigatran caused more gastrointestinal (GI) bleeds but fewer intracranial hemorrhages (ICH) than warfarin. The incidence of dyspepsia is higher with dabigatran and led to a high rate of discontinuation in the premarketing trial.

As an alternative anticoagulant, dabigatran has its limitations and safety concerns. An excess of dyspepsia leads to intolerance and discontinuation. Gastrointestinal bleeding is significantly higher. There is also a potential for accumulation in the presence of renal dysfunction. Lastly, the need for twice a day dosing may negatively impact adherence.

Rivaroxaban has been approved by the FDA for treatment of nonvalvular AF. In the comparison with warfarin, it was equivalent in the ROCKET AF trial which enrolled patients with nonvalvular AF at moderate to high risk of stroke. This agent also has a similar safety profile to dabigatran – higher rate of GI bleeds, lower rate of ICH. Major bleeding was similar between the two treatment groups (3.6% with warfarin vs 3.45% with rivaroxaban). There was a higher rate of bleeding in those over 75, which is also consistent with what was seen in the RE-LY trial with dabigatran. The absolute stroke risk reduction with rivaroxaban was about 0.5 percent with a NNT of 200.

Once daily dosing with rivaroxaban may increase adherence to treatment and patient preference over dabigatran. The safety and efficacy in patients with renal impairment and complex medical illness is not yet clear.

Apixaban is the most recently approved anticoagulant. Apixaban and warfarin were compared in the ARISTOLE trial in AF patients with an average CHADS$_2$ score of 2. This trial was stopped early because of clear efficacy over warfarin based on preset endpoints. The rate of any stroke or systemic embolism was 1.27 percent in the apixaban group versus 1.67 in the warfarin group. Major bleeding occurred in 2.3 percent of the apixaban group versus 3.09 percent of warfarin patients. This is the first of the new medications that shows lower risk of overall bleeding, but this difference was not statistically different. Most of the difference in major bleeding was through decreased ICH. Compared with warfarin, apixaban (over 1.8 years) prevented six strokes, 15 major bleeds, and eight deaths per 1,000 patients treated.

Apixaban has also been compared to aspirin in 6,000 high-risk patients (mean CHADS$_2$ = 2) who were not candidates for warfarin. This trial found superior efficacy of apixaban with similar bleeding rates.

Safety across study groups makes this an attractive option for high-risk bleeding patients. Additionally, because this agent does not require significant renal clearance, it is a good choice for complicated and chronically ill patients. But, there are some issues with apixaban that have to be considered. Apixaban is given twice a day, which may result in lower adherence. Clear superiority over warfarin in an average risk population may not be portable to all risk categories of AF patients.

<table>
<thead>
<tr>
<th>Condition/Regional Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥ 75 years</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>S2</td>
<td>Previous Stroke or TIA</td>
</tr>
<tr>
<td>V</td>
<td>Vascular Disease</td>
</tr>
<tr>
<td>A</td>
<td>Age 65 - 74 years</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex (female gender)</td>
</tr>
</tbody>
</table>
Overall, dabigatran, rivaroxaban and apixaban have demonstrated safety and efficacy in clinical trials. However, real-world and long-term efficacy, safety, and drug interactions have yet to be investigated. While new oral anticoagulants may avoid the burden of regular INR monitoring, bleeding risks and high rates of nonadherence are still a problem. Additionally, there are no established antidotes for the newer agents, thus over-anticoagulation cannot be easily reversed.

Edoxaban (Savaysa®), an investigational factor Xa inhibitor for the prevention of stroke and non-central-nervous-system (CNS) systemic embolism in patients with nonvalvular AF, is under review by the FDA. In one trial comparing this agent to warfarin, low-dose and high-dose edoxaban was noninferior to warfarin and was associated with significantly lower rates of bleeding and death from cardiovascular causes. High-dose edoxaban resulted in more GI bleeding versus warfarin and low-dose edoxaban. This agent will likely be FDA approved in the next year.

Conclusion

Many AF patients, who should be anticoagulated, are not being treated. Because the risk of stroke is significantly elevated in AF, it is important to assess all patients and to prescribe preventive therapies. A variety of anticoagulants can be used to protect against thromboembolic risk in AF. The newer anticoagulants provide clinicians with additional choices for anticoagulation. A need exists for an effective means of stroke reduction that does not expose patients to bleeding events or require long-term patient adherence.

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References

Risk Stratification is a statistical process to determine detectable characteristics associated with an increased chance of experiencing unwanted outcomes. By identifying factors before the occurrence of an event, it is possible to develop targeted interventions to mitigate their impact. Ultimately, the goal of risk stratification is for a health system or insurer to best impact the most patients using limited resources.

Adena Health Systems has a service area of 13 counties in South Central Ohio. With three hospitals and eight regional sites, the system has over 2,800 employees, 220 employed providers, 159 physicians, and 61 mid-level providers. The system also has three Walmart clinics it is involved with. Given their location in the foothills of Appalachia, the system’s service area has some challenges.

Each health system has to consider their population in terms of high-risk, rising-risk, and low-risk groups (Exhibit 1). The small high-risk group has high incidence of disease and significant associated costs. They have complex and late stage chronic diseases such as diabetes and heart failure. The Adena Health Plan covers 4,500 lives with about 20 people accounting for 25 percent of all expenditures. The rising-risk patients are those who have diseases such as diabetes or hypertension, but do not yet have significant complications. The majority of patients will be low risk and relatively well. In 2013, Adena Health Plan had over 1,000 patients with less than $100 annual expenditures each. On one side, this is great to have a large number of people with very low expenditures. On the other side, this may not be ideal because these people may have undiagnosed disease or are not getting preventive care. Thus, population health management using risk stratification is not about managing one population. It’s about managing three—and each requires different goals, resources, and care models.

Exhibit 2 shows a Medicare margin scenario.
which helps explain why it is important to risk stratify. Managing the rising-risk group, in addition to the high risk, will improve a plan’s margin over time rather than a loss of margin. If all resources are allocated to the high-risk group, the rising-risk group will progress to become high risk over time.

On the insurance side, there are tools to help the insurer risk stratify such as claims data. Health plans typically do not have the same data to understand their patients. Thus, plans must do some initial research on their population. The Adena Health Plan did some research on available tools but found they needed to develop their own risk stratification tool. Because this was not being used as a clinical tool, they were not overly worried about it being scientifically validated. It is more a resource management tool. Eventually, the tool was modified to add a diabetes specific stratification (Exhibit 3), which improved predictive ability to identify the rising-risk group. Adena Health Plan had physicians assist in the development of the tool, which improved buy-in from the physicians. This tool was also further modified for the nephrology department to include kidney function to risk stratify their specific population.

After risk stratifying a population, guidelines can be developed or modified to incorporate specific interventions by risk category. In an integrated health system like Adena Health System, the risk stratification guidelines can be incorporated into the system’s electronic medical record. In order to be used, guidelines need to become part of the day-to-day workflow for care providers. Again, physicians have...
to be part of the guideline development process. Additionally, the guidelines need to be evidence-based with references.

Implementation is the next step. As part of a medical home pilot, Adena Health System started with one BS trained nurse navigator in one practice implementing the risk-based guidelines. Eventually, they had nine nurse navigators and four population managers working with 13 practices, including 33 family practice, internal medicine, and pediatric physicians and 20 nurse practitioners. It is now being expanded across all practices in the plan.

Originally medical assistants were used for many tasks related to the guidelines. Assigning these duties to medical assistants significantly impaired workflow within the individual practices. Because many of the tasks were outside the legal practice realm of medical assistants and the workflow issues, the system switched to using population managers. The population managers act on behalf of the physicians under practice agreements. There may be some difficulties in getting physicians to buy into using population managers if the providers perceive a loss of decision control.

In the Adena Health Plan, the population managers are centralized, unlike the nurse managers who are imbedded in individual practices, and do previsit planning and identify gaps in care. A computer system identifies patients with outlying values such as hemoglobin A1C or LDL cholesterol with a risk score to help the managers select patients for intervention.

The impact of risk stratification population man-

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**Exhibit 3: Diabetic Specific Stratification Added**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt; = 7 and &lt; = 7.9</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&gt; = 8 and &lt; = 8.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>&gt; = 9 and &lt; = 9.9</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>&gt; = 10 and &lt; = 10.9</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>&gt; = 11 and &lt; = 11.9</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>&gt; = 12 and &lt; = 12.9</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt; = 100 and &lt; = 130</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&gt; 130</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130/80</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt; 130/80 and &lt; = 140/90</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&gt; 140/90</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Diabetes Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; = 24.9</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt; = 25 and &lt; = 29.9</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>&gt; 30</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Admission to hospital or ED visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>&gt; 1</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

**Risk Stratification**

- **Low Risk** = 0 - 2 points
- **Moderate Risk** = 3 - 5 points
- **High Risk** = 6 - 16 points
agement within a plan has to be measured. Adena Health Plan developed a dashboard that shows pre-visit planning, risk scores, emergency room visits, per member per month outpatient costs, and other measures overall by practice or individual patient. In examining the data, staffing of the nurse navigators can be adjusted based on numbers of high- and rising-risk patients in the various practice sites.

In addition, the program will likely need improvement and modifications. Based on the data, improvement goals can be set for nurse navigators and population managers (Exhibit 4). The people in those actual jobs can develop ways to improve their job. One issue Adena Health System struggles with is patient communication because about half of their population still only has dial-up Internet access. They have their population managers working on ways to improve patient communication.

The financial impact of a population management program also needs to be assessed. For Adena Health System, adding prompts in the electronic medical record and working with their billing department has helped the plan gain more Medicare reimbursement. The use of nurse navigators and population managers has, so far, saved the health system $300,000. The health plan’s primary care medical home led nurse navigation resulted in a drop in the plan’s annual gap insurance costs of more than $100,000.

Conclusion
Population health management using risk stratification provides value to health plans. It can be a hard transition for health systems but is worthwhile. Like any new program, this process requires planning, implementation, measurement of outcomes, and fine tuning of the program.

H. Takaji Kittaka, Jr., MD is the Chief Transformation Officer at Adena Health Systems.

References

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### Exhibit 4: Improvement Goals

<table>
<thead>
<tr>
<th>Nurse Navigators</th>
<th>Individual or Departmental Goals</th>
<th>Metric and Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Expand panel size of patients for assigned primary care practices.</td>
<td>Deficient: Less than 115 patients; Meets: 116 patients to 135 patients; Exceeds: greater than 135 patients.</td>
<td></td>
</tr>
<tr>
<td>2. Provide navigation services to diabetic patients with measurable outcomes hitting the target based on the primary care scorecard, specifically: A1C, LDL, Micro Albumin, Eye Exams.</td>
<td>Deficient: Does not meet targets; Meets: Targets as specified on primary care scorecard; Exceeds: Exceed targets on 2 of 4 metrics.</td>
<td></td>
</tr>
<tr>
<td>3. Reduce utilization of ED and UC visits for assigned primary care practices.</td>
<td>Deficient: Less than 20 visits; Meets: 20 to 26 visits; Exceeds: 27 visits or more.</td>
<td></td>
</tr>
<tr>
<td>4. Research best practices for ED and UC to reduce over utilization and provide recommendations. Provide learning to Inpatient and Ambulatory teams along with physicians.</td>
<td>Deficient: Does not complete research and recommendations; Meets: Complete research, recommendations and develop communication plan for ED/UC by June 1, 2014. Utilization; Exceeds: Completes execution plan for ED/UC Overutilization by September 1, 2014.</td>
<td></td>
</tr>
<tr>
<td>5. Participate in the LEAPT Committee with Quality monthly providing ambulatory navigation recommendations/needs.</td>
<td>Deficient: Attends/Participates at 80% meetings; Meets: Provides opportunity improvements monthly to Nurse Navigation Team; Exceeds: Quarterly LEAPT to PCMH steering committee and two internal medicine practices.</td>
<td></td>
</tr>
</tbody>
</table>
There are multiple types of multiple sclerosis (MS), but the focus tends to be on relapsing-remitting MS (RRMS), which is the most inflammatory and most common of the subtypes. About 70 to 75 percent of patients start out with RRMS. Over time as the inflammation declines, the disease becomes more of a neurodegenerative process with a slow decline (secondary-progressive, SPMS). There are no approved treatments for SPMS. A rarer form of the disease is primary-progressive (PPMS), where patients gradually decline from the outset without any true relapses.

RRMS is an episodic demyelinating disorder with dissemination in space and time that is demonstrated clinically or by MRI. Dissemination in space means there are lesions on MRI in two of the following parts of the nervous system - periventricular, juxtacortical, posterior fossa, or spinal cord. Dissemination in time is met by simultaneous asymptomatic enhancing lesion at the time of the first attack or more than one new lesion (on any follow-up MRI).

As shown in Exhibit 1, activated T cells, B cells, and monocytes attack myelin and nerve fibers in the central nervous system causing MS. The axons get denuded of myelin, which leads to disrupted conduction of signals along the nerve fibers. Myelin is also important for providing a support environment for the nerve fibers.

SPMS is diagnosed based on at least one year of progressive symptoms, plus two of three of the following: one or more lesions in one of the following brain regions: periventricular, juxtacortical, or infratentorial; two or more spinal cord lesions; or oligoclonal bands or elevated IgG index in cerebrospinal fluid.

The area of disease-modifying therapy (DMT) for MS has expanded greatly over the past 10 years. MS therapies have been targeted at modulating the immune system, but we are moving into a new era where hopefully we can restore damaged parts of the nervous system (remyelination) and protect the nervous system, whether inflammation is controlled...
Although many new agents have been approved, the majority of the experience in treating MS is with the older agents (Exhibit 2). Interferons (IFNs) were the first DMTs approved for managing MS. The basic mechanism of action for interferons is a reduction in T cell activation and proliferation. Glatiramer acetate (Copaxone®) produces a shift from a proinflammatory cytokine profile (Th1) to anti-inflammatory profile (Th2). Th1 cells, which produce interferon (IFN)-gamma, interleukin (IL)-2 and tumor necrosis factor (TNF)-beta, evoke cell-mediated immunity and phagocyte-dependent inflammation. Th2 cells, which produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, evoke strong antibody responses (including those of the IgE class) and eosinophil accumulation, but inhibit several functions of phagocytic cells (phagocyte-independent inflammation).¹ Interferons and glatiramer reduce the annualized relapse rate (ARR) in MS by 30 to 40 percent. It is important to note that the untreated relapse rates of the subjects in the studies of older agents such as interferon were much higher than the relapse rates in studies done in the last 10 years. Long-term follow-up of patients on IFNs and glatiramer suggest these drugs are safe and, in some patients, effective for decades. They both reduce disability over time. Longer acting formulations of both have helped reduce the frequency of injection, which helps improve long-term adherence and persistence.

Natalizumab (Tysabri®) is a humanized monoclonal antibody against alpha-4 integrin, a transfer protein needed by immune cells to cross across the blood brain barrier. It was the first novel biologic approved for MS and is the most effective therapy licensed in the United States. It reduces the ARR by 70 percent and the formation of new lesions on MRI in excess of 90 percent. Unfortunately, it has received significant negative press for leading to progressive multifocal leukoencephalopathy (PML), a potentially life-threatening brain infection. This agent does not allow immune cells to cross the blood brain barrier, thus the central nervous system is deprived of immune surveillance. This particular infection is caused by the John Cunningham (JC) virus. Natalizumab was removed from the market for approximately a year and a half but was reinstated under revised guidelines that limit the utility of this very effective agent.

The incidence of PML secondary to natalizumab varies with the length of treatment and JC virus exposure. Those with the least risk are JC virus antibody negative and those with the most risk are antibody positive, with prior immunosuppressive therapy, and receive natalizumab for over 24 months (Exhibit 3). JC virus antibody titers are now available to improve risk prediction; a value less than 0.9 is considered a low positive and low risk. Greater than 1.5 is a high titer, which is higher risk than a low or moderate value.

The first three therapies discussed are only available as injectables. Oral therapies for MS have been
developed to improve patient convenience and possibly adherence. Three such oral therapies have been approved for treating RRMS — fingolimod (Gilenya®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®).

Fingolimod is a sphingosine-1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction. It is an immunomodulator and not an immunosuppressant (i.e., no interference with T cell activation or memory T cell function). In clinical trials, this agent reduced ARR by 50 to 60 percent and MRI evidence of disease activity by 70 to 80 percent compared with interferon and placebo. Disability progression is also reduced by this agent.

Although fingolimod is an effective agent, it does lead to some significant adverse effects. There is clearly an association with life-threatening viral infections. Fatal disseminated varicella zoster virus and herpes simplex virus encephalitis cases occurred in clinical trials and post-marketing.

There are some unique cardiovascular adverse effects of this agent. First-dose bradycardia occurs because the sphingosine-1-phosphate receptor is also involved in the atrial muscarinic-gated potassium channel, which is a key element in vagal regulation of heart rate. A mean decrease in heart rate of 13 beats/min at six hours after the first dose can occur; therefore, patients need to be monitored closely after the first dose. Bradycardia can also occur if therapy is interrupted for a period of time and then the medication is restarted. Atrial ventricular conduction abnormalities (first- or second-degree AV block) also occur in one in 1,000 patients. Sudden deaths, assumed to be related to cardiovascular issues, have been reported in patients receiving fingolimod. Although fingolimod is an effective oral agent that is considered first-line therapy, its side effect profile may outweigh the benefits.

Teriflunomide reduces T cell proliferation, activation, and production of cytokines and interferes with the interaction between T cells and antigen-presenting cells. The effect of teriflunomide on ARR is modest; it decreases ARR by 31 percent compared to placebo. MRI lesion volume is decreased by 39 to 67 percent depending on the dose used and disability is decreased by 24 to 29.8 percent. Although approved in the United States, this agent is not approved in many other countries because of unclear benefit to risk profile.

The major issue with teriflunomide is teratogenicity. It is one of the few medications that can lead to male-mediated teratogenicity, in addition to female-mediated teratogenicity, because of pyrimidine synthesis interference. It can also lead to reactivated tuberculosis; those who are going on this agent should have a screening chest x-ray and PPD before starting. Other adverse effects include diarrhea, nausea, hair thinning, transaminitis, and neuropathy. Because this agent recirculates through hepatobiliary secretion, it can cause adverse effects, including teratogenicity for up to nine months after discontinuation. Given that a significant proportion of RRMS occurs in young women, it may not be the optimal choice for many patients.

Dimethyl fumarate (BG-12) is one of the newest
oral agents approved for MS. It appears to change the balance of Th1 to Th2. It acts more on a genetic level, activating antioxidant and anti-inflammatory pathways and perhaps has neuroprotective properties. It has been licensed in Germany for over 25 years for psoriasis. One minor disadvantage of this agent compared with the other two oral agents is twice a day dosing compared with once a day dosing. The adverse effect profile in MS patients mirrors that in the psoriasis population. Up to 40 percent have gastrointestinal (GI) adverse effects (nausea, diarrhea, cramping). The cramping can be very difficult to control. The average duration of GI adverse effects persisting is three to six months but can last up to two years. Flushing, transaminitis, leukopenia, and proteinuria can also occur. Compared to placebo, BG-12 leads to a 50 percent reduction in ARR, a 34 to 38 percent reduction in risk of disability progression, and a 74 to 90 percent reduction in MRI lesions. When compared to glatiramer acetate and placebo, ARR was reduced by 44 percent versus placebo in the lower-dose group, 51 percent in the higher-dose group, and 29 percent in the glatiramer acetate group.

Laquinimod is an investigational quinolone compound that affects Th1/Th2 balance without clear immunosuppressant action and may decrease antigen presentation. Currently this agent is not approved in the U.S. or Europe, but it is still being evaluated for the MS indication. In one major trial comparing it to placebo in RRMS, the ARR was decreased 21.3 percent (p=0.026), which is very modest. The reason this agent is still being considered are its possible neuroprotective effects. In the trial, there was a 33.5 percent decreased risk of disability progression (p=0.044) and a 27.5 percent reduction in brain volume loss (p<0.0001).

Several therapies are emerging as possible MS treatments. These include alemtuzumab, daclizumab, and ocrelizumab. Additionally numerous agents are under investigation specifically as neuroprotective agents.

Alemtuzumab is currently approved for B cell chronic lymphocytic leukemia in the U.S., and RRMS in the majority of areas outside of the U.S. It is an anti-CD52 humanized monoclonal antibody that depletes B and T cells. In a trial comparing alemtuzumab to high-dose IFNβ-1a (Rebif®) there was a 55 percent reduction in relapse rate for alemtuzumab-treated patients versus IFNβ-1a. In a Phase III trial of patients who had relapsed on therapy, there was a 49 percent reduction in ARR (p<0.000) and a 42 percent reduction in sustained. This agent does have a significant adverse effect profile. The major adverse effects are autoimmune B cell related adverse effects, including idiopathic thrombocytopenic purpura and autoimmune thyroid disease. Regular complete blood counts are required for monitoring.

Daclizumab, another agent under study, is a humanized monoclonal antibody against the alpha subunit of the IL-2 receptor (CD25) on T cells,
which reduces T cell activation and proliferation and expands CD56 bright cells that inhibit T cell survival. The major adverse effect seen in trials with this agent is rash. Others reported include nasopharyngitis, upper respiratory infection, headaches, and transaminitis. It does not appear to be associated with infections or malignancy. In a Phase 2b trial comparing daclizumab to placebo, the ARR was decreased by 50 percent in one year. Typically more than one year is required to show a difference in ARR. Eighty percent of daclizumab-treated patients and 64 percent of placebo patients were relapse free. Disability progression was reduced by 50 percent, raising the possibility of neuroprotective effect. On MRI, there was about an 80 percent reduction in new lesions. Reduction in disability progression was independent of relapses, and is one of the most noteworthy findings from the study.

B cells play a role in the pathogenesis of MS and also have a downstream effect on T cell function. Rituximab, a monoclonal antibody targeted against CD20 B cells, has been studied in RRMS with good effects on ARR and MRI lesions. This agent was not pursued for an MS indication because the cost was significantly more than the possible benefit compared with other agents. An agent that acts the same way, ocrelizumab, is currently under study. When compared to placebo and interferon, 80 percent of those treated with ocrelizumab were relapse-free, 76.4 percent had no disease progression, and the ARR was reduced in patients switched from placebo and interferon. Additionally, there were no new MRI lesions in the treated group. Like most targeted therapies, adverse effects are the issue, including PML and other infections.

Optimal utilization of MS therapies goes beyond suppression of relapses and MRI activity alone. It requires patient adherence with therapy even when they are feeling well. Adherence can be improved with counseling about potential adverse effects and prompt management of any adverse effects which occur.

Conclusion
MS therapeutics is a dynamic field which continues to expand. Each therapy comes with some downsides that have to be addressed with patients. Many clinicians start with the traditional first-line therapies because of the length of experience with them, saving the newer agents for later use. Clinical symptoms and MRI findings remain mainstay methods for assessing success and disease progression. Symptomatic management of adverse effects and patient counseling are required to facilitate long-term adherence.

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References

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IN THE UNITED STATES, 68.5 PERCENT OF adults aged 20 years or older are overweight and 34.9 percent are obese. Body mass index (BMI) is used to classify the degree of excess weight (Exhibit 1). BMI is highly correlated with the percentage of body fat on a population basis and as BMI increases the health risks associated with body fat also increase. These health risks are numerous (Exhibit 2). In general, greater BMI is associated with increased rate of death from all causes and from cardiovascular disease; this is particularly true for those with extreme obesity.

Given the health consequences of excess weight, weight loss is very important. A small reduction in excess body weight (5% to 10%) has been shown to dramatically improve glucose and blood pressure.

Lifestyle changes are first line for managing excess weight. Decreasing energy intake by at least 500 calories per day can help people lose a pound per week. A review of randomized, controlled trials compared diets with varying macronutrient compositions and found that caloric restriction rather than macronutrient composition is the key determinant of weight loss. Although there are numerous specialty diets touted for weight loss, in general, all diets produce comparable weight-loss results if patients stay on them. Thus, adherence to a diet is the best predictor of weight-loss success rather than the actual type of diet a patient eats. After three to six months, adherence to most diets tends to wane. In addition to motivation waning, the body also makes physiologic adjustments that work against losing weight.

Physical activity is a key part of treatment, but it is not as effective as diet for acute weight loss. The real role for physical activity is for weight maintenance. Sixty minutes of moderate-intensity activity most days of the week is needed to prevent weight regain.

When patients are evaluated for weight loss, it is...
important to examine what medications the patient is currently receiving. Medications can cause weight gain or loss or be weight neutral (Exhibit 3).9 Within the antipsychotic medications, olanzapine (Zyprexa) induces the most weight gain and ziprasidone (Geodon) the least. Offending medications should be eliminated if possible.

In addition to lifestyle changes and medication adjustments, many patients will need weight-loss medications to achieve sufficient weight loss. In 1947, the FDA approved the first prescription obesity medication, methamphetamine. In 1973, the FDA, concerned about the abuse potential of the amphetamines, limited the indication of obesity medications to short-term use. Several decades later dexfenfluramine (1996), sibutramine (1997), and orlistat (1999) were approved. Dexfenfluramine was removed from the market in 1997 because of concerns about cardiac valve damage and sibutramine was removed because of possible increase in cardiovascular risk in 2010.

Weight-loss medications are indicated as an adjunct to diet and exercise in adults with BMI $\geq 30$ kg/m$^2$ or $\geq 27$ kg/m$^2$ and weight-related comorbidities. It is important to note that weight-loss medications only work in conjunction with lifestyle changes.

Noradrenergic sympathomimetic drugs are approved for short-term use (up to 12 weeks), but these are commonly used long term. These agents reduce food intake by causing early satiety and stimulate release of norepinephrine or block its reuptake. Approved noradrenergic drugs include phentermine, diethylpropion, benzphetamine, and phendimetrazine. Phentermine is the most prescribed agent in the U.S. These agents can all increase blood pressure and heart rate and are contraindicated in those with cardiovascular disease. Additionally, there are concerns about abuse potential.

In order for a drug to be approved for the long-term treatment of obesity, it must meet certain benchmarks for weight loss relative to placebo: mean weight loss $\geq$5 percent more than that of the placebo group or proportion of drug-treated participants who lose $\geq$5 percent of initial weight is $\geq$35 percent and approximately double the proportion who lose $\geq$5 percent in the placebo group at one year.10 Exhibit 4 compares the three agents (orlistat, lorcaserin, phentermine/topiramate) approved for long-term use.

Orlistat works by binding to gastrointestinal lipases, preventing hydrolysis of dietary fat (TGs) into absorbable free fatty acids and monoacylglycerols. It is taken three times per day during or up to one hour after meals and leads to the excretion of approximately 30 percent of ingested fat. It is available in prescription (120 mg) and over-the-counter (60 mg) strengths. Orlistat 120 mg is FDA approved for use in adults and adolescents (aged 12 to 16 years). Studies have demonstrated that orlistat-treated subjects who completed trials lasting one year lost approximately 9 percent of their pre-intervention body weight, as compared with 5.8 percent with placebo. In long-term studies, orlistat-treated patients also had moderate decreases in diastolic blood pressure, fasting insulin levels, and lipids, with a small cholesterol-lowering effect that was independent of weight loss.11-13

Orlistat in combination with lifestyle changes has been studied for the prevention of type 2 diabetes in obese patients in a four-year, double-blind, prospective study. Orlistat use decreased body weight over four years by 2.7 kg ($\approx$2.4% of initial body weight) more than placebo and significantly decreased risk for developing type 2 diabetes from 9.0

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**Exhibit 1: Classification Based on BMI**

<table>
<thead>
<tr>
<th>BMI kg/m$^2$</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 18.5$</td>
<td>Underweight</td>
</tr>
<tr>
<td>$\geq 18.5 - 24.9$</td>
<td>Normal Weight</td>
</tr>
<tr>
<td>$\geq 25.0 - 29.9$</td>
<td>Overweight</td>
</tr>
<tr>
<td>$\geq 30$</td>
<td>Obesity</td>
</tr>
<tr>
<td>30.0 - 34.9</td>
<td>Class I Obesity</td>
</tr>
<tr>
<td>35.0 - 39.9</td>
<td>Class II Obesity</td>
</tr>
<tr>
<td>$\geq 40$</td>
<td>Class III Obesity, extreme, severe, morbid obesity</td>
</tr>
</tbody>
</table>
percent with placebo to 6.2 percent with orlistat. The medication’s mechanism of action leads to increases in undigested stool triglycerides and therefore generating considerable gastrointestinal side effects, which causes many patients to discontinue the treatment. Fewer than 10 percent of patients prescribed the medication take it for at least one year and less than 2 percent take it for two years.

Lorcaserin is a selective serotonin 2C (5HT2c) receptor agonist that decreases food intake. This agent has the weight-loss effects of dexfenfluramine, which is a nonselective serotonergic agonist, without the adverse cardiac effects such as valvulopathy thought to be mediated by agonism of the 5HT2B receptor. Lorcaserin 10 mg BID was FDA approved in 2012 on the basis of two large randomized, placebo-controlled trials in nondiabetic patients and a third smaller trial in adults with type 2 diabetes.

In one trial of lorcaserin, 47.5 percent of patients receiving lorcaserin had lost 5 percent or more of their baseline body weight at one year, as compared with 20.3 percent of those receiving placebo (P<0.001). Those in the lorcaserin group lost an average of 5.81 percent of the baseline body weight, as compared with 2.16 percent in the placebo group (P<0.001). For those in the lorcaserin group who had lost ≥5 percent at year one, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year two than in those who were reassigned to receive placebo (67.9% vs. 50.3%, P<0.001).

Phentermine plus topiramate-extended release is the first FDA approved combination for obesity, combining low-dose phentermine with a low dose of the antiepileptic medication topiramate. Weight-loss clinicians had been using these two medications in combination for some time before the combination product was improved. The combination was approved in 2012 based largely on two trials. In one of the trials, 84 percent of subjects completed two years of treatment with sustained weight loss of 9.3 percent at the recommended dose (7.5 mg phentermine/46 mg topiramate) and 10.5 percent at a highest dose (15 mg/92 mg) compared with 1.8 percent for placebo. There was a lower rate of development of type 2 diabetes in those who received the combination.

Topiramate can cause oral clefts in the offspring of women who become pregnant while taking it. Women with childbearing potential should have a negative pregnancy test prior to starting phentermine/topiramate and be tested monthly thereafter. This restriction limits the use of this combination. A small increase in resting heart rate has been observed in the clinical trials of phentermine/topiramate at higher doses, with more patients on topdose (56.1%) than placebo (42.1%) having increases
of more than 10 beats per minute, leading to some concerns regarding its potential long-term effect on cardiovascular events.

The three agents approved for long-term use, when prescribed with lifestyle interventions, produce additional weight loss relative to placebo, ranging from approximately 3 percent of initial weight for orlistat and lorcaserin to 9 percent for phentermine/topiramate at one year. The proportion of patients achieving clinically meaningful (at least 5%) weight loss ranges from 37 to 47 percent for lorcaserin, 35 to 73 percent for orlistat, and 67 to 70 percent for phentermine/topiramate. These medications produce greater improvements in many cardiometabolic risk factors than placebo and reduce the development of type 2 diabetes, but none has
been shown to reduce cardiovascular morbidity or mortality.\textsuperscript{10} It is important to note that people will regain much of the weight lost when weight-loss therapies are discontinued.

**Conclusion**

The incidence and prevalence of obesity continues to grow. Lifestyle changes are first line for reversing excess weight. Because many medications can lead to weight gain, clinicians need to consider changing to medications that are more weight neutral or promote weight loss. Two new weight-loss therapies have been approved which can help people lose weight.

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