To the Editor: A recent article by Ross et al1 reported the results of comprehensive genomic profiling of cancers of unknown primary (CUPs) and documents frequent occurrence of clinically relevant genomic alterations. We describe herein the outcome of a case of CUP, which may serve to illustrate both the benefit of personalized therapy and potential pitfalls.

A man in his 60s presented with CUP involving bones and lymph nodes. He had a history of stage II testicular seminoma, treated with orchectomy and radiation therapy, and this disease had been in remission for 5 years. Bone pain led to the diagnosis of multiple lytic bone metastases. Excisional biopsy of a supravacular node demonstrated poorly differentiated adenoscarcma. Immunohistochemistry and gene expression profiling and positron emission tomography were inconclusive for the primary site. The patient was empirically treated with carboplatin and paclitaxel with a good clinical and radiographic response. After initiation of chemotherapy, results of tumor genomic profiling became available. Erbb2 amplification and a BRCA1 mutation were found. Therefore, trastuzumab was added to the last 2 cycles of chemotherapy and continued as maintenance therapy. After completion of chemotherapy, lapatinib was prescribed in addition to trastuzumab. Two years after diagnosis of CUP, the patient remained free of disease progression or symptoms.

Although this patient’s disease responded well to chemotherapy, durable remission after chemotherapy is rare in CUP. Bone metastasis is associated with poor survival in CUP.2 Therefore, it is tempting to attribute the unusually long progression-free interval to Erbb2-directed maintenance therapy with trastuzumab and lapatinib. The tumor also harbored a mutant BRCA1 allele, which was independently detected by our institutional research study of tumor genome sequencing (UNCSeq: NCT01457196).3 The patient was referred to genetic counseling, and standard genetic testing confirmed him to be a germline carrier of a common BRCA1 founder mutation, 5385insC (formerly 5382insC).4 The wild-type allele of BRCA1 was retained in the tumor, and it is unclear whether the tumor is predisposed to respond to therapy targeting BRCA1 loss of function. Tumor profiling led to the diagnosis of his germline BRCA1 mutation, which raised serious implications for his child’s risk of cancer and their decisions regarding genetic testing. Tumor genomic profiling may yield additional treatment options with long-term clinical benefit. However, clinicians and patients should be made aware that there may be unanticipated consequences for patients and their families from detection of germline variants.

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To the Editor: In their February 2015 article on genomic profiling of cancers of unknown primary (CUP), Ross et al1 state that 149 of 200 CUPs harbored “clinically relevant genomic alterations” with the conclusion that “comprehensive genomic profiling shows promise to identify targeted therapeutic approaches to improve outcomes for this disease.” We respectfully suggest that their definition of “clinically relevant” may be overly inclusive and therefore impractical for oncologists caring for patients with CUP at this time.

The most common alterations that were reported to be clinically relevant were in KRAS, CDKN2A, and MCL1. Despite a few promising small studies of MEK inhibition in KRAS-mutant lung cancer, targeted therapies directed at mutant RAS have generally been unsuccessful, and there is little compelling evidence that CDKN2A and MCL1 are actionable targets.5 It is also unclear how the authors have confirmed a diagnosis of CUP given the lack of reported clinical information. Samples are included in the study with TMPRSS2-ERG and EML4-ALK fusions, samples that the authors themselves note should be excluded because they suggest likely primary prostate and lung cancers, respectively. We agree that the endless search for a primary is unlikely to change treatment for most patients. However, by including patients with a likely primary site of disease such as lung cancer in CUP reports such as this, the authors risk simply reporting the excellent responses to targeted therapies seen in appropriately selected patients with those cancers.

We agree with the authors on several points. Patients with CUP have been subjected to unnecessary diagnostic tests with medical, emotional, and financial costs. They have been underestimated by clinical research in which trial eligibility typically requires a known primary site of disease and potentially have much to gain from “basket studies” in which patients receive targeted therapies based on the presence or absence of specific genomic alterations. Furthermore, knowledge in this field is changing rapidly, and mutations that are not clinically relevant today may be relevant tomorrow. We are leading a research effort to perform comprehensive genomic profiling for patients with CUP at our institution to determine whether these results can inform treatment decisions and, most importantly, to learn whether these informed decisions do or do not ultimately lead to improved clinical activity and improved patient outcomes. We are hopeful that

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comprehensive genomic profiling will improve outcomes for patients with CUP through precision use of targeted therapies; however, this is a hypothesis that needs to be tested.

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To the Editor We would like to commend Ross et al1 for undertaking this important work because carcinoma of unknown primary (CUP) represents a fertile ground for the implementation of molecular therapeutics. Because no standard therapy exists, CUP presents a unique opportunity to use comprehensive genomic profiling to guide targeted therapy as an initial treatment. However, we would like to comment on 2 specific concerns.

First, the authors suggest that we should abandon the practice of identifying primary tumor sites, on the basis of the premise that this diagnostic evaluation is expensive and often uninformative.2 We believe that a focused evaluation to find the tumor origin, potentially incorporating genomic profiling, remains important for a select group of patients and should not be disregarded. An illustrative example from our CUP clinic at the University of Michigan demonstrates this concept: we elected to pursue a repeat biopsy for a woman in her 70s who presented with abdominal carcinomatosis. Her initial diagnosis was adenocarcinoma of unknown origin on the basis of peritoneal fluid cytologic analysis; however, an ovarian biopsy revealed that the tumor was likely of Mullerian origin via immunohistochemical analysis. Because optimal surgical debulking has been demonstrated to confer survival benefit in this setting,3 we referred the patient for operative intervention. Although we concur that tumor origin diagnostics are usually not informative, we must be careful not to neglect information that may alter therapy for a small number of patients. Our challenge is thus to identify creative, cost-effective methods to select patients for whom this information matters. We must also not forget that patients often wish to know the origin of their cancer given that lack of a definitive diagnosis can be disconcerting.

Second, whereas this study provides evidence that targetable genomic alterations can be identified in the CUP population, trials are warranted to determine whether delivery of targeted therapy will indeed improve outcomes. In addition, we advocate for a study that incorporates genomic profiling at diagnosis, such that patients might receive biomarker-driven therapy as the initial treatment for their cancer. In addition, a recent study of more than 400 patients with diverse cancers who underwent next-generation sequencing highlighted that increasingly, many of the actionable mutations may be targetable with an already approved drug (albeit usually off-label).3 No targeted therapies are currently approved for use in CUP, and the off-label prescribing of these medications poses numerous challenges. Therefore, a multicenter trial incorporating access to targeted therapeutics already approved for use in other malignant neoplasms (ie, BRAF, EGFR, ALK inhibitors) for patients with CUP is imperative.

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In Reply We read with interest the 3 Letters to the Editor in response to our study on the potential impact of using comprehensive genomic profiling early in the management of patients presenting with cancer of unknown primary source (CUP).4 We believe that the 3 letters, in different ways, enhance the discussion of our study as the transition from one-size-fits-all nontargeted chemotherapy to genomic-driven targeted therapy continues. The letter from Cobain et al from the Universities of Michigan and California at San Diego cites the importance of considering appropriate surgical procedures in some forms of cancers initially presenting as CUP. We agree completely that Mullerian tract–derived cancers such as serous carcinomas within the abdominal cavity should be surgically debulked whenever possible. In our study,4 we attempted to limit the criteria for CUP to exclude cases in which surgical treatment was immediately needed at the time of presentation, which, in most cases, included a broad nondiagnostic immunohistochemical (IHC) workup before the diagnosis of CUP was conferred. We also agree with Cobain et al that all targeted therapies are “off-label” for patients with a diagnosis of CUP and that genomically driven clinical trials for
patients with CUP are needed. We thank Varghese and Saltz from Memorial Sloan Kettering Cancer Center for their comments concerning the definition of “actionability” in the setting of cancer presenting as CUP.

Also, in response to Varghese and Saltz, TTF1-positive tumors with EML4-ALK fusions characteristic of non-small-cell lung cancer were not included in our series. One case in our series did feature a TPMRSS-ERG fusion diagnostic of metastatic prostatic carcinoma. This case was listed as a CUP in that the tumor did not mark by IHC analysis as being of prostatic origin and the clinical workup did not suggest that the patient had prostate cancer. Although not a focus of our present study, we believe that hybrid capture-based comprehensive genomic profiling can definitively identify the site of origin in approximately 10% to 15% of CUP cases. The case example in our article of an EML4-ALK fusion cancer responding dramatically to crizotinib therapy cannot, in our opinion, be designated as a lung cancer by current diagnostic criteria because IHC analysis was negative for TTF1, positive for vimentin, and featured a poorly differentiated, nonmucinous, sarcomatoid morphologic appearance. Finally, we thank Whang and Hayes from the University of North Carolina for their letter describing the prolonged response of a patient to an anti-human epidermal growth factor receptor 2 plus chemotherapy regimen for an ERBB2-amplified CUP. Finally, our article1 and all 3 Letters to the Editor have in common the desire to see the development of mechanism-driven prospective clinical trials in which genomic profiling is used to search for “druggable” alterations in CUP cases to achieve a comparison of the results of the use of targeted therapies when possible with generic chemotherapy and testing whether this approach can improve the clinical outcomes for patients with this devastating form of cancer.

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The Demanding Patient Revisited

To the Editor We read with interest the study by Gogineni et al,1 in which oncologists recalled a patient request or demand in less than 9% of 5050 visits. Furthermore, only 1 in 9 requests or demands was deemed inappropriate. The authors concluded that demanding patients are infrequent in oncologic practice. They contrasted their results with the findings of Kravitz et al,2 which identified patient requests for tests, referrals, or prescriptions in 23% of visits. To explain the discrepancy, Gogineni et al speculated that coding of transcribed audio recordings may exaggerate the frequency of requests relative to oncologist report, that “in California, primary care patients make more demands than cancer patients in Pennsylvania,” and that our study had fewer encounters and clinicians, “generating a selective sample.”3

Although we agree that “demanding patients” cannot be held responsible for a large share of cancer-related costs, the following qualifications merit attention. First, considering the high stakes of a cancer diagnosis and patients’ deep dependence on their oncologists, a rate of requests approaching 1 in 11 seems anything but low. Second, physician recall (especially when elicited up to 4 hours after the visit) is an insensitive measure, especially in comparison with direct observation and coding by trained reviewers of visit transcripts.3 Patient-reported request rates are higher still,4 in part because patients’ requests often use indirect linguistic forms that may be missed or misinterpreted by physicians.5 Third, a sample drawn from 3 tertiary care hospitals in Philadelphia hardly seems less selective than one drawn from primary care and cardiology practices in California. Finally, oncologists in tertiary centers already offer a full slate of aggressive diagnostic and therapeutic services. Few patients would have a need to request services that are already on offer.

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To the Editor As a cancer patient and advocate, I was happy to read the Editorial by Back6 discussing the study by Gogineni et al7 published in JAMA Oncology on February 12. It is comforting to know that a study was performed to address this issue as opposed to allowing the stereotype to persist that patients cause financial strains on the health care system with our requests for “unnecessary” treatment. As a multiple myeloma patient (6 years post-diagnosis this St Patrick’s Day), I can attest to the value of the partnership between an attentive, inquisitive medical professional and an informed patient as it relates to proper diagnosis, treatment, and follow-up care.