

## VIEWPOINT

# Reducing Overtreatment of Cancer With Precision Medicine

## Just What the Doctor Ordered

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**Clinicians increasingly recognize** the problem of overtreatment in medical care. Overtreatment is particularly a concern for cancer conditions that are targeted for early detection because screening results in a large population of patients with early-stage disease. Patients with early-stage disease may experience overtreatment because the cumulative morbidity and adverse consequences on quality of life of cancer therapies are often substantial, but the benefit of each single modality can be very small and uncertain in an individual patient. For example, the net 10-year survival benefit of chemotherapy for patients with node-negative, hormone-receptor positive, *ERBB2*-negative (formerly *HER2* or *HER2/neu*) breast cancers smaller than 2 cm is less than 4%.<sup>1</sup> Prior to the advent of genomic expression testing, professional consensus guidelines for treatment diverged from those of a National Institutes of Health/Centers for Disease Control and Prevention panel strongly recommending adjuvant chemotherapy in these patients, whereas an international panel was not supportive of this approach.

In contrast to those undergoing chronic disease management, patients newly diagnosed with cancer have little time to learn about the disease and its management because they often have multiple treatment options directed by different specialists they generally meet for the first time. Furthermore, the clinical information that informs treatment evolves rapidly over time; and for many patients, the clinical consequences may worsen after diagnosis because the cancer is found to be more extensive after further evaluation. For patients with breast cancer, an initial diagnosis of carcinoma in situ on core biopsy may be reclassified as invasive disease after surgical excision requiring consideration of systemic therapies; findings of breast magnetic resonance imaging may suggest more extensive disease prompting more biopsies; tumor margins may be deemed insufficient after initial lumpectomy triggering discussion about reoperation; and identification of metastasis to regional lymph nodes after mastectomy may motivate a discussion about the need to add radiation therapy to the treatment course. In addition, the increasing use of multiple-gene sequencing tests for patients with breast cancer exposes patients to potentially ambiguous information about future risk of a second primary cancer and new concerns regarding the risk of cancer developing in family members. This cascade of information may be emotionally difficult for patients and increase their desire to avoid future cancer recurrence at any cost.

Addressing the potential for overtreatment with patients after a diagnosis of cancer is challenging.

Patients fear cancer and often dread the arduous treatment course that lies ahead. Uncertainty about the disease and its management is disturbing to patients and can evoke powerful psychological reactions that frequently increase patients' desire for more extensive treatment than may be clinically indicated. For example, *anticipated regret* describes patients' fear of forgoing the most aggressive treatment now and experiencing a future disease recurrence. The *possibility effect* describes the strong psychological reaction to a very small potential gain that deviates from futility (eg, 0% to 3% benefit). This is a common problem in decisions about the use of systemic chemotherapy for patients with early-stage breast cancer because net benefit is often very small. *Confirmation bias* is the tendency to disregard potentially useful information that conflicts with existing beliefs. In clinical encounters, confirmation bias can limit a patient's attention to useful information about net benefit of a treatment option if that information conflicts with immediate emotional reactions.

While there is much research on these underlying intuitions that drive patient preferences, few strategies are available to help guide clinicians in addressing these psychological reactions with patients. Physicians' responses to patient reactions vary markedly.<sup>2</sup> Physicians may be concerned that resisting patient desires may decrease satisfaction. They also may be vulnerable to intuitions such as anticipated regret, triggered by recall of patients they have treated previously who have experienced disease recurrence, which may make those physicians reluctant to limit treatment. Physicians may defer to patients' desires for more extensive treatment than may be necessary because they perceive that pursuing such treatment may reduce decision conflict or emotional burden. In addition, physicians may conflate patients' immediate reactions to disease and prospects for treatment with long-term well-being. Taken together, the complicated dynamic of these communication and decision factors is not conducive to addressing overtreatment during brief encounters.

Precision medicine most effectively reduces overtreatment because it can remove a more extensive treatment option from consideration if that treatment is deemed by clinicians to be futile. Precision medicine in cancer uses information derived from patient factors (age, comorbidity, and, increasingly, genetic predisposition) and characteristics of the diagnosed tumor to quantify the net benefit of a treatment option in an individual patient. The 3 steps to harnessing precision medicine to address overtreatment are (1) increasing the evidence base for less vs more extensive treatment in

key clinical subgroups; (2) formulating more precise clinical algorithms to tailor treatment to the relevant subgroup; and (3) ensuring consensus among clinicians with regard to applying the algorithm to individual patients.

Breast cancer is a model for how precision medicine has reduced uncertainty for many patients with early-stage disease and consequently has reduced overtreatment. Growing concerns of clinicians about overtreatment in breast cancer have spawned initiatives to evaluate the equivalence of less vs more extensive treatments for patients with early-stage disease. Over the past 5 years, clinical guidelines from cancer professional organizations have been promulgated that recommend (1) limiting reoperation after initial lumpectomy<sup>3</sup>; (2) decreasing the use of axillary lymph node dissection after a positive sentinel node biopsy<sup>4</sup>; (3) reducing the inconvenience and extent of irradiation<sup>5</sup>; and (4) omitting adjuvant chemotherapy for patients with early-stage disease with favorable characteristics.<sup>6</sup>

The growing evidence base supporting less morbid treatment strategies has been applied to individual patients by physicians using more precise test algorithms. The evaluative test cascade—which includes both clinicopathologic features (histology, tumor size, and nodal status) and tumor biology testing (hormone receptor status, *ERBB2*, and molecular assays)—can identify which patients will benefit from adjuvant chemotherapy with more certainty. The algorithm is increasingly less vulnerable to unwanted variability in analytic and clinical validity as well as interpretation of results by physicians. Clinicians have used the algorithms to increasingly recommend against more extensive treatment in patients with favorable disease characteristics. A steep persistent decline in use of systemic chemotherapy for patients with early-stage breast cancer is the result of oncologists using an algorithm to identify patients for whom the administration of additional treatment would do more harm than good.<sup>7</sup> A recently documented substantial decline in mastectomy (including bilateral mastectomy) serves as an important ex-

ample of how greater precision applied to clinicopathologic features can markedly reduce overtreatment. Reoperation after lumpectomy is common, and a substantial number of patients who undergo reoperation subsequently receive mastectomy. A published guideline underscored strong consensus that emerged among surgeons and radiation oncologists regarding management of surgical margins after lumpectomy in patients with invasive disease.<sup>3</sup> The consensus was associated with a marked decline in reoperation after lumpectomy,<sup>8</sup> which consequently reduced rates of mastectomy in an era during which rates had been increasing.<sup>9</sup>

Even though patients contribute to the potential for overtreatment, clinicians are ultimately responsible for addressing it during clinical encounters. The paradox of precision medicine is that as clinical algorithms become more precise, they become more complex for physicians and patients. Thus, it is not surprising that patients increasingly desire that their clinicians help them navigate treatment decisions. This responsibility motivates the need to improve clinician skills in patient-centered communication with regard to explaining the evidence for recommendations and addressing patient reactions to the disease and management plan. But improving clinician communication skills alone will have little effect on reducing overtreatment. A key lesson from encounters with breast cancer is that physicians can harness advances in precision medicine to reduce the burden on patients of unnecessary treatment. These advances include new technologies of tumor biology-based benefit stratification but also better evidence for the more accurate assessment of traditional clinicopathologic features of disease. Together they provide the tools a clinician needs to recommend against a treatment that does more harm than good for an individual patient. More research will be needed to examine potential disparities in how these advances such as multiple-gene sequencing are used. Breast cancer will continue to be emblematic of how advances in precision medicine can reduce the burden of disease 1 patient at a time.

#### ARTICLE INFORMATION

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