

## Precision Medicine Core: Progress in Prognostication— Populations to Patients

Carolyn Compton, MD, PhD

Scottsdale, Arizona

“Prediction is very difficult, especially if it’s about the future.”

Niels Bohr (1885–1962), Theoretical Physicist and Nobel Laureate

Prognostication is fundamental to the practice of medicine. For the patient, it goes to the heart of their primary concern. What will happen to me? How likely am I to survive or die? For the physician, it shapes decision making and management strategy. For others, such as translational researchers, population scientists, payors, and healthcare analysts, it helps to classify patients into meaningful groups for comparison. Despite its essential role, prognostication is one of the most challenging tasks in cancer medicine.

The complexity of prognostication is directly related to the complex biological nature of both cancer itself and the individual patient in which it arises. It is further complicated by man-made prognostic factors referable to the medical environment in which the patient is managed and the medical teams administering the care. Like all biological entities, cancer is classified as a complex adaptive system, characterized by unpredictable behavior and the emergence of new properties as it evolves. It is comprised of innumerable parts but is also more than the sum of its parts. Given these daunting realities about the very nature of cancer, it could be argued that accurate predictions of outcome are impossible. At present, this may be true. However, like forecasting the weather, another complex adaptive system, predictive accuracy can be improved by advanced data collection techniques, information science, and analytical innovation. We are moving forward on all

these fronts in oncology and look forward to greater accuracy in prognostication as these disciplines converge.

Progress in precision medicine has accentuated the need for more accurate, individualized prognostication tools. We have, as an oncology community, undertaken deliberate efforts to identify and validate key variables that inform prognosis (‘prognostic factors’ or ‘patient classifiers’) and develop computational approaches that integrate these variables into algorithms that increasingly improve outcome prediction for cancer patients (‘risk calculators’). However, overall, such efforts have been largely uncoordinated, decentralized, and highly variable in terms of specific content, intended context of use, and development methodology. Authoritative developmental guidelines for prognostication tools that would help to assure quality, consistency, and utility have also been lacking. As a result, the value of existing prognostication tools varies widely.

The American Joint Committee on Cancer (AJCC) is the global leader in developing cancer staging systems, which serve as essential patient classifiers. The utility of these staging systems is directly linked to their correlation with patient outcomes, and stage has long been regarded as the most powerful prognostic factor for most adult malignancies. On a biological level, its power is undoubtedly related to its surrogacy for the extent of tumor evolution, complexity and heterogeneity. However, prognostic correlates for any given TNM stage grouping are based on data from large populations of cancer patients, expressed as the average of a range of outcomes for a given stage, and have limited application to an individual cancer patient. The AJCC has long recognized the need to improve prognostication and risk stratification for individual patients beyond anatomic stage alone, and in the 7th edition of its staging manual began to incorporate selected individual non-anatomic prognostic factors into stage grouping tables. However, in the process of developing the 8th edition of the Cancer Staging Manual, the growing need for individualized prognosis aligning with the vision of precision

oncology was reassessed. It was acknowledged that a more comprehensive approach was required that incorporated stage and other key prognostic factors into a computational tool that could more precisely predict outcome for individual patients.

In response, the AJCC established an expert group called the Precision Medicine Core (PMC) to take the first steps to meet this need and to lead the AJCC in the sponsorship and development of high-quality prognostication tools for cutting-edge oncology practice. Rather than developing and validating such tools from scratch, the AJCC first decided to analyze all existing prognostication calculation tools for major cancer sites according to a fixed set of quality criteria for tool development that it would define prospectively through expert consensus.<sup>1</sup> Although developed independently, the AJCC quality criteria were consonant with those defined by a separate international initiative entitled Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD).<sup>2</sup> Using the newly developed quality criteria as a guideline, the PMC evaluated existing prognostication tools for major cancer sites. Tools that met all criteria were endorsed by the AJCC for use by the cancer community and were included in the relevant chapters in the 8th edition of the AJCC Cancer Staging Manual.<sup>3</sup> By the time of the publication deadline, prognostication models identified and evaluated by the PMC numbered 27 for breast cancer, 37 for colorectal cancer, 16 for prostate cancer, 7 for melanoma, 4 for soft tissue sarcoma, and 19 for selected hematologic malignancies. However, those meeting all quality criteria were few: specifically, 2 for breast, 3 for colorectal cancer, 2 for prostate cancer, 1 for soft tissue

sarcoma, and none for melanoma or hematological malignancies. The PMC is continuing its reviews of tools for other cancer sites and will be posting the evaluations on the AJCC website on an ongoing basis. Through this process, meritorious tools will be identified, and gaps in tool availability will become apparent to inform new tool development, including that by the AJCC itself. The highlighting of vetted, high-quality prognostication tools is envisioned as a service for, and unmet need of, the cancer community. The AJCC plans to support this effort in perpetuity and review new tools as they are developed over time. Focusing on high-quality data and computational tool design, and keeping pace with new data, technologies, and methodologies, the AJCC intends to provide inspiration and leadership for a new era of prognostication in cancer medicine—prognostication that moves beyond populations to individual patients.

## REFERENCES

1. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin*. 2016;66:370–4
2. Moons KG, Altman DG, Reitsma JB, Collins GS. Transparent reporting of a multivariate prediction model for individual prognosis or development initiative. New guideline for reporting of studies developing, validating or updating a multivariate clinical prediction model: The TRIPOD statement. *Adv Anat Pathol*. 2015;22:303–5.
3. Amin MB, Edge SB, Greene FL, Schilsky RL, Gaspar LE, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.