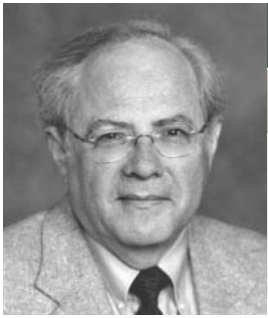

INTERVIEW

Norman Wolmark, MD

Dr Wolmark is Chairman of the NSABP at Allegheny General Hospital in Pittsburgh, Pennsylvania and Professor of Human Oncology at the Drexel University College of Medicine in Philadelphia, Pennsylvania.

Tracks 1-8

Track 1 NSABP-C-07 study: Validation of the Onco*type* DX Colon Cancer assay RS as a predictor of recurrence risk in patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without oxaliplatin

Track 2 QUASAR: Validation study results for the Onco*type* DX Colon Cancer assay for prediction of recurrence risk in Stage II colon cancer

Track 3 Use of the Onco*type* DX RS to assist in tailoring treatment decisions for patients with early colon cancer

Track 4 Complexities in the use of adjuvant oxaliplatin for localized colon cancer

Track 5 Utility of the Onco*type* DX and ColoPrint assays

Track 6 Use of oxaliplatin in patients aged 70 or older

Track 7 Development of an Onco*type* DX Treatment Score for prediction of benefit with oxaliplatin

Track 8 NSABP-C-10: Results from a Phase II study evaluating mFOLFOX6 in combination with bevacizumab for patients with unresectable metastatic colon cancer and a synchronous asymptomatic primary tumor

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you provide your perspective on the role of the Onco*type* DX Colon Cancer assay in the management of Stage II and Stage III disease?

DR WOLMARK: The QUASAR study prospectively validated the Onco*type* DX Recurrence Score as a predictor of recurrence risk for patients with Stage II colon cancer (Gray 2011). Patients were randomly assigned to surgery with or without fluoropyrimidine-based chemotherapy, excluding oxaliplatin. About 40% of the surgery-alone cohort fell into the low-risk category and had a 12% recurrence risk at 3 years. The intermediate-risk group had an 18% recurrence risk, whereas the high-risk group, which constituted about 25% of the study cohort, had a 22% recurrence risk. This study demonstrated that not all patients with Stage II disease are the same and that a spectrum can be categorized to reflect low, intermediate and high recurrence risk groups.

The NSABP-C-07 trial confirmed the value of the 12-gene Onco*type* DX Colon Cancer Recurrence Score as a predictor of recurrence risk in patients with Stage II and III colon cancer treated with 5-FU/leucovorin with or without the addition of oxaliplatin (O'Connell 2012; [3.1]). The Recurrence Score does not predict response to chemotherapy, but it was associated with outcome independent of other discriminates like nodal status and tumor grade.

DR LOVE: Although the QUASAR study showed that the Onco*type* DX assay was not predictive of benefit from chemotherapy, it seems that you can determine an absolute benefit from chemotherapy and differentiate patients who will have, for example, a 3% absolute relapse risk reduction and others with an 8% benefit. Can you comment on this aspect?

DR WOLMARK: This is definitely true of the QUASAR study and gets to the crux of how the algorithm can be applied. The proportional reductions in risk of recurrence with chemotherapy were similar across the range of Recurrence Scores. However, a patient with a low likelihood of recurrence has a smaller absolute benefit from chemotherapy than one with a high risk of recurrence.

It is noteworthy that in the NSABP-C-07 trial we can make the same observation. Even though the hazard ratio for the addition of oxaliplatin was similar across groups, patients in the low-risk cohort obtain little benefit from the use of oxaliplatin. The NSABP-C-07 study provides objective data to determine what the absolute benefit of adjuvant oxaliplatin will be to guide treatment decisions.

3.1

Validation of the Onco*type* DX Colon Cancer Recurrence Score (RS) in the Phase III NSABP-C-07 Study as a Predictor of Recurrence in Patients with Stage II and Stage III Colon Cancer Treated with 5-FU/Leucovorin with or without Oxaliplatin

		Five-year recurrence risk by RS	
		5-FU	5-FU + oxaliplatin
Stage II	Low RS	7%	12%
	Intermediate RS	8%	10%
	High RS	23%	9%
Stage IIIA/B	Low RS	19%	17%
	Intermediate RS	30%	19%
	High RS	43%	31%
Stage IIIC	Low RS	41%	38%
	Intermediate RS	48%	40%
	High RS	67%	59%

Conclusions: "RS predicts recurrence risk in Stage II and III colon cancer, capturing underlying biology and providing risk information beyond conventional factors. RS is not predictive of relative benefit of oxaliplatin added to adjuvant 5-FU but enables better discrimination of absolute oxaliplatin benefit as a function of risk. For certain patients with Stage IIIA/B disease, the finding of low RS (<30), and thus low recurrence risk and low absolute oxaliplatin benefit, may not justify the risk of potential toxicity from adding oxaliplatin."

O'Connell M et al. *Proc ASCO* 2012;**Abstract 3512**.

Tracks 4-5

DR LOVE: We presented a poster at the 2013 Gastrointestinal Cancers Symposium on the results from a survey of 102 US-based oncologists regarding the use of adjuvant oxaliplatin in 408 patients with Stage II and III colon cancer. Surprisingly, there was a high rate of oxaliplatin use for patients with Stage IIB disease and elderly patients, aged 70 and older, with Stage III colon cancer (Love 2013; [3.2]). What are your thoughts about usage of adjuvant oxaliplatin?

DR WOLMARK: I believe that the use of oxaliplatin for Stage II colon cancer can be challenged based on the data from the QUASAR and NSABP-C-07 studies. Patients at high risk derive a greater benefit from oxaliplatin whether they have Stage II or Stage III disease. So the risk must be considered in addition to whether the patient has Stage II or Stage III colon cancer. Even though the relative recurrence risk across the entire continuous variable for the addition of oxaliplatin is the same, the absolute benefit varies dramatically from low-risk to high-risk groups.

Oxaliplatin is an effective agent in the adjuvant setting for colon cancer. However, it's associated with neurotoxicity, and around 15% to 20% of patients have some residual neurotoxicity. So we have to be mindful of that. If a patient at high risk was reluctant to take oxaliplatin, I would try to convince him or her to take it as part of the regimen. However, in the low-risk group, where the absolute benefit is much smaller, one can justify not administering oxaliplatin based on the results of the NSABP-C-07 study.

DR LOVE: Does the Onco*type* DX Colon Cancer assay have a role outside a protocol setting?

DR WOLMARK: I believe this assay has a role outside a research setting. The Onco*type* DX 21-gene assay is used for more than 60% of women with node-negative, ER-positive breast cancer in the United States and has led to a decrease in the use of adjuvant chemotherapy in this population. In colon cancer we've seen reluctance to embrace the Onco*type* DX assay, which has been validated and confirmed, provides prognostic information and is useful in making treatment decisions. ■

3.2

Is Adjuvant Oxaliplatin Overused in Colon Cancer? 408 Cases from the Practices of 102 Oncologists

	Stage II (N = 306)					Stage III (N = 102)	
Adjuvant treatment	T2 N = 16	T3 N = 229	T4 N = 61	Age <70 N = 200	Age ≥70 N = 106	Age <70 N = 84	Age ≥70 N = 18
None	12 **75%**	142 **62%**	5 **8%**	78 **39%**	81 **76%**	1 **1%**	1 **6%**
5-FU	1 **6%**	11 **5%**	3 **5%**	11 **5%**	4 **4%**	0 **0%**	0 **0%**
Capecitabine	2 **13%**	32 **14%**	13 **21%**	31 **16%**	16 **15%**	4 **5%**	1 **6%**
Oxaliplatin/ fluoropyrimidine	1 **6%**	44 **19%**	40 **66%**	80 **40%**	5 **5%**	79 **94%**	16 **88%**

Love N et al. Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

SELECT PUBLICATIONS

Gray RG et al. **Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer.** *J Clin Oncol* 2011;29:4611-9.

Kelley RK, Venook AP. **Prognostic and predictive markers in stage II colon cancer: Is there a role for gene expression profiling?** *Clin Colorectal Cancer* 2011;10(2):73-80.

Love N et al. **Is adjuvant oxaliplatin (Ox) overutilized in colon cancer (CC)? 408 cases from the practices of 102 oncologists.** Gastrointestinal Cancers Symposium 2013;**Abstract 479**.

O'Connell MJ et al. **Validation of the 12-gene colon cancer Recurrence Score result in NSABP C-07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (5FU) and 5FU/LV + oxaliplatin (5FU+Ox).** *Proc ASCO* 2012;**Abstract 3512**.