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EDITORIALS

Precision Medicine for Cancer Patients: Lessons Learned and the Path Forward

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An explosion in our knowledge of cancer biology has occurred in the decade since the elucidation of the human genome. The potential for translation of this genomic information to the therapeutic management of patients has generated great excitement, although, despite some stellar successes, progress has been slower than expected. However, the concept of personalized or "precision" medicine that integrates genomic knowledge (such as molecular analysis of the patient's tumor) and other laboratory research with input from health records, along with social and environmental data, for the selection of the optimal therapy for the individual patient remains attractive. Striking examples of success with this approach are the use of *BCR-ABL* mutations to predict clinical responses to imatinib in chronic myelogenous leukemia and *EGFR* mutations to predict clinical response to *EGFR* tyrosine kinase inhibitors in non–small cell lung cancer. These approaches use "enrollment biomarkers" to identify mutant targets to attack with specific therapies. An example of a newly recognized potential enrollment marker is expression of the SLFN11 gene for prediction of sensitivity to topoisomerase inhibitors (1). Another approach is to use tumor mRNA expression patterns, "molecular signatures," for response prediction for the selection of conventional cytotoxic therapies. Enrollment biomarker approaches are mechanistically based in that they are directly related to the targeted pathway and thus directly connect the therapy to the tumor's "oncogene addiction." Tumor mRNA phenotypes, however, have not been shown to directly relate to the targeted tumor pathway(s) or addiction in most cases. Thus, such approaches are less specific and often rely on gene panels whose mechanistic roles and relevance are not apparent. All such approaches may be facilitated by preclinical models (e.g., tumor cell lines, xenografts, and genetically engineered mouse models of cancer) for which both molecular analyses and therapy response phenotypes can be determined independent of the patient and which can lead to the development of molecular signatures predictive of response to specific therapies. This latter approach permits the widespread, unbiased testing of new therapies and their correlation with molecular markers. Such preclinical models also allow for totally independent testing by multiple investigators of proposed therapies and their molecular correlations and for systematic genetic (e.g., small interfering RNA or short hairpinRNA) and chemical library-wide searches for "tumor acquired vulnerabilities" (synthetic lethalities) to identify previously unknown cancer therapies that have specificity for tumor over normal tissues and also specificities for subtypes within tumors of the same primary type. These approaches are being used by programs such as the National Cancer Institute's (NCI's) Cancer Target Discovery and Development (CTD) Network (2) as well as many pharmaceutical and biotechnology companies.

In this issue of the Journal, Wang et al. (3) address an important related issue: how to evaluate the clinical relevance of a drug sensitivity signature developed from a preclinical model without knowledge of all relevant information. The US-based academic authors collaborated with a Danish pharmacodiagnostic company, which developed a drug response predictor for the relevant cancer therapeutic drugs using the NCI-60 panel of cell lines (4). The academic group scoured the literature to find all deposited tumor databases that had used a single commercial gene expression microarray and had at least 100 patients with the same type of cancer who had received the same treatment and for whom clinical outcome information was available. When this information was coupled with only those drugs used in the treatment for which information from the NCI-60 datasets met criteria for analyses, only three datasets were finally available: one each for breast cancer, Hodgkin's lymphoma, and acute lymphoblastic leukemia. The relative paucity of datasets with appropriate clinical and response information should indicate to investigators and funding agencies the importance of generating more of these vital components. Using the NCI-60 cell line panel data, the pharmacodiagnostic company generated gene lists for prediction of response to the academic team in "locked down" mode (i.e., no further modifications permitted), and the academic team used the gene lists to generate scores predictive of response. Although the overall findings of Wang et al. (3) indicated that the model prediction was "better than chance", the biomarker scores "added little to existing clinical predictors; statistically significant contributions were likely to be too small to change clinical practice." Because of the unusual nature of the study, we (and, presumably, the academic authors) were not provided with details of how the gene lists were generated, and the methodology cannot be evaluated except by its performance. In addition, it should be noted that the provenance and relevance of the long-established NCI-60 panel have been questioned, and its application to hematopoietic tumors not included in the panel is problematic. Although the use of cell line panels offers many benefits (5), fresh approaches for their generation and use for translational applications may be required (6).

Although the contributions of the report by Wang et al. (3) toward developing new precision medicine approaches for cancer

patients are modest, the article and the authors' previous contributions have highlighted many important points that merit further discussion. These include important issues that will have considerable impact on the design, execution, and interpretation of similar omics approaches for therapy selection and related applications. This editorial continues the discussion begun in a previous editorial we wrote for the Journal focused on lung cancer (7).

First, we want to strongly take issue with one of the reasons that Wang et al. cited for conducting their study (3). The authors developed their "black box" approach without having full access to the gene selection methodology because they suggest that inventors of omics-based tests may want to deliberately withhold data for propriety reasons. Although this may in fact occur, individuals, institutions, and commercial entities may file for patent protection for their inventions. However, it is crucial that the scientific community demand full disclosure of all relevant data and procedures before publication. Without full disclosure, validation studies and clinical applications should not occur. The requirement for absolute and full disclosure is best illustrated by the recent example of three clinical trials initiated at Duke University Medical Center for gene expression–based selection of therapy for cancer patients. The trials, which were flawed by problems of failure of full disclosure, computational errors, and outright fraud, received considerable coverage in the scientific and popular presses (8,9). Not only did patients fail to get the promised "best individualized therapy," in at least some cases they may have received the predicted least effective therapy. Possibly the greatest error was the collective failure of an estimated 400 participating investigators, university officials, journal editors, and funding agency staff to heed the many warnings of independent experts, including Kevin Coombes and Keith Baggerly (10,11), two of the authors of the Wang et al. report (3), for a period of about 3 years. However, a major benefit to result from this debacle was that the Institute of Medicine was tasked by the NCI to determine "the lessons learned and the path forward" (12). We highlight some of the salient findings in the report.

Translation of omics-based findings requires full discloser and access to computer code and the complex computational procedures required for development of the test procedure. Guidelines for authors to provide sufficient information for independent verification have been detailed by Coombes and Baggerly (10,11). All testing of patient samples should be performed in Clinical Laboratory Improvement Amendments–certified laboratories. Perhaps the most important recommendation of the Institute of Medicine report was that clinical applications of omics-based research were a major responsibility that was shared between the investigators, their institutions, sponsors of the research, and the scientific journals. Institutions and sponsors unwilling or unable to assume this major responsibility should not support such research. As part of this this process, the Food and Drug Administration should be closely consulted and should play a proactive role for any clinically used test.

In conclusion, we are excited by the progress and opportunities for developing precision medicine for selection of therapy for individual patients and reemphasize the importance of 1) the development and availability of clinically and molecularly annotated patient tumor datasets; 2) further development and use of large preclinical models and their datasets for multiple tumor types; and most important, 3) establishment of a translational/clinical research culture where rigorous experimental design, methodology, execution, proper validation with full transparency, and disclosure leading to an atmosphere of shared responsibility is regarded as an absolute necessity. The path forward will be greatly eased if we have learned from our lessons.

References

1. Barretina J, Caponigro G, Stransky N, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*. 2012;483(7391):603–607.
2. Cancer Target Discovery and Development Network, Schreiber SL, Shamji SF, et al. Towards patient-based cancer therapeutics. *Nat Biotechnol*. 2010;28(9):904–906.
3. Wang W, Baggerly K, Knudsen S, et al. Independent validation of a model using cell line chemosensitivity to predict response to therapy. *J Natl Cancer Inst*. 2013;105(17):1284–1291.
4. Shoemaker RH. The NCI60 human tumour cell line anticancer drug screen. *Nat Rev Cancer*. 2006;6(10):813–823.
5. Gazdar AF, Girard L, Lockwood WW, et al. Lung cancer cell lines as tools for biomedical discovery and research. *J Natl Cancer Inst*. 2010;102(17):1310–1321.
6. Gillet JP, Varma S, Gottesman MM. The clinical relevance of cancer cell lines. *J Natl Cancer Inst*. 2013;105(7):452–458.
7. Gazdar AF, Schiller JH. Predictive and prognostic factors for non–small cell lung cancer—potholes in the road to the promised land. *J Natl Cancer Inst*. 2011;103(24):1810–1811.
8. Kaiser J. Clinical medicine. Biomarker tests need closer scrutiny, IOM concludes. *Science*. 2012;335(6076):1554.
9. CBS News. Deception at Duke: fraud in cancer care. CBS News. February 12, 2012. http://www.cbsnews.com/8301-18560_162-57376073/deception-at-duke-fraud-in-cancer-care/. Accessed July 22, 2013.
10. Baggerly KA, Coombes KR. What information should be required to support clinical "omics" publications? *Clin Chem*. 2011;57:688–690.
11. Coombes KR, Wang J, Baggerly KA. Microarrays: retracing steps. *Nat Med*. 2007;13(11):1276–1277; author reply 1277–1278.
12. Institute of Medicine. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. http://www.iom.edu/Reports/2012/Evolution-of-Translational-Omics.aspx. Accessed July 22, 2013.

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