On the cusp of a revolution: Melanoma molecular diagnostics

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As part of the celebration of the Academy’s 75th anniversary, this year each monthly issue of JAAD features an expert commentary on a previously published article of particular significance to practicing dermatologists.

“It would not be surprising...if one day it were shown that the causes and pathogenesis of malignant melanomas at different anatomic sites and those that arise de novo, rather than in association with melanocytic nevi (MN) are very different.”

Adele C. Green, 1992

“We now understand that it is not sufficient to identify a tumor based on histology or the organ or origin as we have done traditionally but rather we now need to understand the particular molecular driver of the tumor and select the appropriate therapy.”

Michael Link, President of ASCO, 2012

Vast changes have occurred over the last two decades in our understanding of melanoma, which has moved from a “black box” to a tumor driven by genomic instability, aberrant signal transduction pathways, and stem cell phenotype. Indeed, a core of genetic abnormalities that define specific subtypes of melanoma has been identified such as mutant BRAF in melanomas from intermittently sun-exposed skin (superficial spreading melanoma), mutant or amplified C-KIT in melanomas of chronically sun-damaged skin (lentigo maligna melanoma), cyclin D1 (CCND1) amplification in acral melanomas, and mutant GNAQ in uveal melanoma.

In the last 8 years, the diagnostic, prognostic, and therapeutic molecular biomarkers and targeted therapies envisaged in “Molecular Diagnostics in Melanoma” are becoming a reality. These recent, significant progresses in the prediction, diagnosis, prognosis, and treatment of melanoma include, respectively, molecular testing for germline mutations associated with increased melanoma susceptibility; array comparative genomic hybridization (aCGH) and fluorescent in situ hybridization (FISH) methods that can classify the majority of ambiguous melanocytic proliferations; gene expression profiling that can stratify melanoma patients into prognostically relevant groups; and Food and Drug Administration (FDA)–approved therapies for metastatic melanoma: ipilimumab, which enhances tumor-specific immunity, and vemurafenib, which targets mutant BRAF melanoma (in conjunction with its FDA-approved companion diagnostic test).

This molecular diagnostics revolution will rapidly evolve because of advances in technology and the promise of cheap, whole genome data. Like Moore’s law for computational power, one can anticipate discovery of novel melanoma-related genes;
improved accuracy of testing; less expensive, but more powerful molecular assays; and novel, specific, less toxic single or combinatory therapies every several years. These innovations and the expansion of molecular biomarkers will improve the outcomes for melanoma patients. The biomarkers that will facilitate this paradigm shift can be classified based on the hallmarks of melanoma, which are acquired via genomic instability and mutation\textsuperscript{4,5}: 1) self-sufficiency in growth signals; 2) insensitivity to anti-growth signals; 3) evasion of apoptosis; 4) limitless replicative potential; 5) tissue invasion and metastasis; 6) angiogenesis; 7) escape from immune surveillance and hormonal control; and 8) altered melanocyte differentiation program.

One up-and-coming innovation of molecular diagnostics will be the advent of “next generation sequencing” (NGS). NGS with its increased sensitivity, decreased expense (“the less than $1000 genome”), and greater ability to provide whole genome analysis (WGA) promises to produce “actionable” genomic aberration data that will predict sensitivity or resistance to approved or standard therapies, or those that are inclusion or exclusion criteria for specific experimental therapies in National Cancer Institute (NCI) registered trials. Overall, these new methods, new markers, and better understanding of melanoma will allow for improved outcomes and, at the very least, control/management of melanoma as a chronic disease. The current task will be to determine and validate how, when, and where this WGA can replace standard sets of molecular diagnostics utilized today. In addition, the incorporation of molecular diagnostics in dermatology curricula should be implemented quickly to ensure that residents are familiar with applications of up-to-date dermatology laboratory—based tests and to keep pace with the rapidly evolving field of molecular diagnostics.\textsuperscript{6}

REFERENCES