The dermatopathologist's role in genetic testing for hereditary cancer syndromes: Utility versus patient liberty

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CASE SCENARIO

You are a dermatopathologist at a large academic medical center. A clinician in your department submits a shave biopsy specimen from a 33-year-old woman with a yellow papule on the nasal ala, concerning for basal cell carcinoma. According to the requisition, she has no personal or family history of skin cancer; no other family history is recorded. On review of the biopsy specimen, you find a dermal tumor comprised of basaloid germinative cells with admixed sebocytes. You sign out the case as sebaceous adenoma.

Several days later, your clinician colleague calls you asking to have microsatellite instability (MSI) testing performed on the specimen. Although many dermatopathology laboratories may perform this testing reflexively, yours does not. Upon review of the chart, you notice that the patient has not yet been notified of the histologic diagnosis, nor the implications of a possible hereditary cancer syndrome, namely Muir-Torre. When asked about this, your colleague states that the patient is recently married and planning to conceive. He does not want to discuss the potential reproductive ramifications of this syndrome with her until it is confirmed with genetic testing.

What is the most ethically appropriate action?

A. Perform MSI testing on the tissue per your colleague's request.
B. Do not perform the testing until your colleague discusses it with the patient and obtains informed consent.
C. Call the patient yourself, discuss the implications of testing, and proceed if she consents.
D. Request that another dermatopathologist perform the testing on the case for the clinician.

DISCUSSION

This case illustrates the dermatopathogist's dilemma related to performing genetic testing on skin specimens that may be associated with hereditary cancer syndromes. Because, in most clinical settings, consent is sought for genetic testing, the role of informed consent in testing for MSI or in immunohistochemistry (IHC) for hereditary cancer syndromes on skin biopsy specimens is debated.[1,2] A second issue highlighted in this case is ambiguity in the dermatopathologist-patient relationship, in which the pathologist may feel dual, at times conflicting, obligations to the clinician and the patient. This analysis will explore the ethics of MSI and IHC testing for hereditary cancer

Abbreviations used:

IHC:	immunohistochemistry
MSI:	microsatellite instability
MTS:	Muir-Torre syndrome

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syndromes on skin biopsy specimens. Specifically, it will discuss arguments for and against informed consent in this setting using utilitarian and libertarian approaches, respectively. Further, the analysis will review the merits of informed consent pursued directly by the pathologist with the patient.

ANALYSIS OF CASE SCENARIO

Muir-Torre syndrome (MTS) is an autosomal-dominant hereditary cancer syndrome characterized by sebaceous neoplasms, including sebaceous adenomas, epitheliomas, and carcinomas, in addition to internal malignancies, most commonly colorectal cancer. MTS is considered a subtype of hereditary nonpolyposis colorectal cancer or Lynch syndrome, with which it shares the same defect in DNA mismatch repair. Germline mutations in the DNA mismatch repair system, specifically in MSH2, MSH6, and MLH1, are observed in over 95% of associated tumors.[3]

As MSI and loss of heterozygosity has been shown in about 66% of the aforementioned sebaceous neoplasms, testing of these tumors is important in the workup of MTS.[4] The clinical implications of a diagnosis of MTS for the dermatologist include early referral to gastroenterology for colorectal cancer screening, regular skin examinations for other skin neoplasms commonly encountered in this syndrome (eg, keratoacanthomas), consideration of oral retinoids for chemoprophylaxis, and counseling about appropriate screening in family members.

Although genetic testing is routinely performed on sebaceous tumors, guidelines for informed consent before testing have not been formalized. For Lynch syndrome, recent recommendations from the Evaluation of Genomic Applications in Practice and Prevention Working Group clearly call for informed consent before testing on colorectal carcinomas, given the potential implications for the patient and family members.[1] This recommendation has been met with recoil by some bioethicists, given that the testing alone may carry psychosocial hazard for the patient, even if the result is ultimately negative.[2] Furthermore, if MSI/IHC testing reveals evidence of mismatch repair mutations, germline mutation testing must then be completed for confirmation. This testing generally requires formal informed consent given that a germline mutation reveals information about a patient herself, rather than a resected tumor. Despite the recommendations of the working group, colorectal tumors are routinely MSI/IHC tested to assess for Lynch syndrome without patient consent.

A similar practice holds for many laboratories in evaluating for MTS, as sebaceous tumors are often reflexively MSI/IHC tested. However, the approach to sebaceous neoplasms is more nuanced, given that a diagnosis of MTS may be made in the absence of family history of associated tumors. Further, a patient with cutaneous findings alone may be young without any other signs or symptoms of the syndrome. The probability of finding other manifestations of MTS with a new sebaceous tumor is variable.

Dermatopathologists may face conflicting pressures in considering genetic testing on skin biopsy specimens, given their concomitant professional obligations to patients and clinicians. For example, dermatopathologists often make additional diagnostic or treatment recommendations in scenarios in which they may be more familiar with the disease process than the clinical dermatologist, such as in rare cutaneous neoplasms or with genetic testing recommendations for which they may have received specialized training.[5]

Conversely, clinical interventions recommended by pathologists may be problematic in other scenarios, such as common cutaneous malignancies, in which dermatopathologist and clinician treatment recommendations may differ. This conflict may manifest in genetic testing as the dermatopathologist may be more familiar than the clinician with what testing on the tissue specimen entails and how to interpret results. However, the clinician may have a better sense of how the results of testing might affect the individual patient. Both physicians may have the patient's best interest in mind, but may reach different recommendations. In this case, potential resolutions include further discussion with the clinician to elucidate the patient's values and an attempt to come to a mutually agreed-upon plan of action, or direct discussion with the patient by the pathologist, as explored in option C (see below).

Option A, in which the dermatopathologist conducts MSI testing without involving the patient, seems most common in practice. Given that MSI uses variability in lengths of microsatellite markers as a surrogate for defects in DNA mismatch repair mechanisms, it may be ethically