February issue of AJSP.[1] The authors pointed out the potential value of the *V600E* and *NRASQ61R* mutation–specific antibodies in recognizing dedifferentiated metastatic malignant melanoma.[2] The authors also presented a case of metastatic dedifferentiated melanoma known to harbor the *NRASQ61R* mutation, and they showed expression of the *NRASQ61R* mutation–specific antibody in the metastasis by immunohistochemistry (IHC).

We thank Uguen and colleagues for their interest in our study and for emphasizing that point, with which we fully agree. Although many recent studies showed a 100% specificity and sensitivity of these next-generation antibodies as surrogate molecular markers,[3] a considerable fraction of cases show discrepant results, and a second-round IHC was needed for increasing the concordance rate, as the authors themselves admitted in a recent study.[4] Discrepancies between IHC and direct sequencing are, at least in part, related to some technical issues as reflected by varied results among different laboratories. Further, the results and thus the sensitivity and specificity seem to be influenced by the tissue (melanoma vs. colorectal carcinoma).[5] In this context, we like to draw attention of the authors and the readers to a very recent study by Turchini et al[6] who examined a large cohort of colorectal cancer specimens (n = 2823) and found that the *NRASQ61R* antibody detects not only the *NRASQ61R* but also specifically detects the *KRASQ61R* mutation. Taken together, these new observations underline the need for caution when using emerging antibodies as surrogate molecular markers, as the specificity of many of these antibodies has not been sufficiently explored yet.

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Phenotype of Hepatocellular Neoplasms Associated With Androgen Use

To the Editor:

In their recent study on hepatocellular neoplasms arising in association with androgen use in 9 patients, Gupta et al[1] state that their report is the first to investigate in detail the histopathologic and immunohistochemical features of these lesions.

We would like to mention that we recently described 3 β-catenin-activated hepatocellular neoplasms in a patient who received androgens for treatment of Fanconi anemia,[2] of which 1 was considered as an adenoma and 2 as well-differentiated hepatocellular carcinoma (HCC) arisen in an adenoma. Adding our cases to those of Gupta et al,[1] the tumors of 8 of 10 patients showed a β-catenin-activated phenotype. Although there is no single consistent phenotype across all cases, as stated by Gupta et al,[1] molecular alterations in the β-catenin pathway appear to be a dominant feature of adenomas and adenoma-derived liver tumors in this special setting. At least, there is much more molecular homogeneity compared with similar tumors arising in other special settings, such as in glycogen storage disease type 1.[3]

Another recurring feature of these lesions appears to be the presence of a cholestatic phenotype. Bilirubinostasis was reported in 6 of 9 cases by Gupta et al,[1] and we reported bilirubinostasis, feathery degeneration, and diffuse expression of cytokeratin 7, all hallmarks of cholestasis, in 1 of 3 tumors.[2] This is especially noteworthy, as liver adenomas arising outside the setting of androgen use only rarely show cholestasis.[4] It has been suggested that adaptations of the hepatobiliary transporter profile helps to prevent the development of cholestasis in the absence of bile ducts.[4] Moreover, it has been reported that drug-induced liver injury with bilirubinostasis due to androgenic steroids could be related to inhibition of the *ATP8B1* transporter.[5] Altogether, we feel that there is enough evidence to suggest that interference of androgens with hepatobiliary transport function plays an important role in the pathogenesis of hepatocellular neoplasms occurring in the setting of androgen use. Gupta et al[1] mention that there are yet-to-be-identified initial mutations in these tumors driven by androgen use, and we therefore think that hepatobiliary transporters should be the main focus of further research.

Our case report was published shortly before the proposal of the new diagnostic category "hepatocellular neoplasm of uncertain malignant potential" or HUMP.[6] Using the criteria proposed by Bedossa et al,[6] the lesion we designated as cholestatic adenoma can be considered as a cholestatic HUMP because of the presence of β-catenin activation. As the 2 other

lesions were characterized by the combined presence of considerable to extensive reticulin loss and cytologic atypia and immunohistochemical evidence of β-catenin activation, we feel that our diagnosis of well-differentiated HCC developing in adenoma remains valid, rather than designating these lesions as HUMP. Gupta et al[1] designated all their lesions as HUMP, which was partly based on the fact that these tumors have excellent prognosis and can regress after cessation of androgen use. Their choice is surely defendable, but given the description of the presence of cytologic and architectural atypia in >5% combined with immunohistochemical evidence of β-catenin activation in some of the lesions they reported, one can argue that the term well-differentiated HCC rather than HUMP is applicable to these lesions. This is an illustration of the ongoing discussion regarding the criteria of the diagnostic category HUMP,[7,8] which includes the validity of the 5% cutoff for atypia and the ambiguity of the terms focal and patchy. Very recent data suggest that the rate of tumors placed in the HUMP category is too high using current criteria.[9] Detailed morphologic, immunohistochemical, and molecular studies of more cases of liver tumors arising in the setting of adrogen use combined with long-term follow-up will be needed to definitely resolve this discussion.

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Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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