A Plea for Biobanking of All Equivocal Melanocytic Proliferations

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In 2005, in an editorial in the Archives of Dermatology (now JAMA Dermatology), we made a plea for a combined diagnostic approach to histopathologic and dermoscopic evaluation.1 We concluded our editorial with the following statement1(p211):

Histopathology, as every other purely morphologic method, is limited by methodologic drawbacks and sometimes by practitioners' personal limitations. Today we are on the edge of a new biology in histopathology, and one can foresee that our beloved classic morphology will soon be replaced by new technologies. In the meantime, a combined morphologic approach linking dermoscopy and histopathology might be helpful for pathologists to come to more reliable diagnostic conclusions for patients and their physicians.

And it is encouraging to see that indeed there is an increased awareness by colleagues dealing with problematic and borderline melanocytic proliferations that has led to a more refined clinicodermoscopic and pathologic approach in the interpretation of these lesions.

In the present editorial, we take the opportunity to make another plea, namely, a plea for biobanking of all equivocal melanocytic proliferations. This plea is based on our interpretation of the pioneering study by Malvehy and colleagues2 in this journal.

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In the present editorial, we take the opportunity to make another plea, namely, a plea for biobanking of all equivocal melanocytic proliferations. This plea is based on our interpretation of the pioneering study by Malvehy and colleagues2 in this issue of JAMA Dermatology. This original morphologic study combining expertise in dermoscopy and dermatopathology will doubtless lead to a redefinition of the way traditional gross pathologic procedures are carried out for equivocal pigmented skin lesions. We commend the authors of this seminal, albeit contested, work, and we agree with them that highly specialized providers of skin pathologic analysis will embrace more advanced sampling technologies that use dermoscopy guidance in the future, thus reflecting the paradigmatic shift from conventional surgical pathologic analysis to molecular pathologic analysis, in order to remain competitive and, most importantly, do the most good for our patients.

Why Biobanking?
The new credo of personalized medicine has already reached dermatology, and more and more of our patients with melanoma are no longer asking about their prognosis or about an estimated survival time but whether their melanoma is a BRAF melanoma. Whereas this specific query can be answered rather easily by performing, for example, the cobas 4800 BRAF V600 Mutation Test (Roche) on formalin-fixed paraffin-embedded samples, there is a growing need for frozen tissue samples for those molecular and genetic tests that might be available by the time today's primary melanoma metastasizes in 5 or 10 years' time. There is no doubt that biobanking is one of the central tools for clinical and translational medicine.3 The challenge is, of course, to organize the biobank sampling with minimal disruption to the busy daily practice of dealing with patients with melanomas and clinically suspicious pigmented skin lesions. Malvehy and colleagues2 correctly note that their sophisticated protocol for biobank sampling has been developed for "experienced research centers." Of interest is a recent publication by Caenazzo and colleagues4 on the ethical issues of balancing the rights of the individual and the interest of society in biobanking research on oncological residual material. Biobank research cannot be conducted without considering arguments for obtaining the donors' consent. The authors described the type of consent that "would be appropriate in this context, considering the ethical principles of donation, solidarity, protection of the donors' rights and the requirements of scientific progress."4 The authors concluded that an important ethical aspect in regard to the role of biobanking is the need to encourage sample donation.

Dermoscopy, Dermatopathology, and Targeted Sampling
The "ex vivo dermoscopic-oriented sampling of melanoma" protocol has been designed in close collaboration by a group of dermatologists and dermatopathologists, all of them with great expertise in dermoscopy, with the specific aim of not jeopardizing the conventional histopathologic diagnosis. The protocol includes conservation of the thickest part of the lesion for measuring the Breslow index. The authors nicely showed that by creating a "dermoscopic melanoma map" they were able to successfully sample the nonthickest part of the lesion and also avoided sampling areas that contain dermoscopic melanoma-specific features whose absence could interfere with the dermatopathologist's ability to render a conclusive diagnosis. Unfortunately, their targeted sampling protocol excludes small melanomas, dermoscopically equivocal lesions, and other melanocytic lesions for which they suspect that the histopathologic evaluation may prove difficult. The authors fear that insufficient material will be provided for the pathological assessment and that this may lead to clinical and medicolegal consequences.5 Also, the issue of shave biopsies or saucerizations was not mentioned at all. Only completely excised lesions can be included. All these exclusion criteria are, in our estimation, serious limitations for the purpose of "biosampling" even in...

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a highly specialized melanoma center because as many suspicious melanocytic skin proliferations as possible should be biosampled. However, one can imagine that, inspired by this original and authentic work by Malvehy and colleagues, several dermatology and/or pathology teams worldwide will come up with their own solutions and protocols for molecular sampling of suspicious melanocytic proliferations.

**Microbiopsies for Molecular Sampling**

Recently, we have developed a submillimeter skin punch biopsy device for minimally invasive and suture-free skin sampling that extracts approximately 1500 keratinocytes and 5 to 10 ng DNA and RNA for molecular diagnosis in dermatology and dermato-oncology (L. L. Lin, BSc; T. W. Prow, PhD; A. P. Raphael, PhD; R. L. Harrold III, MD; C. A. Primiero, BSc; A. B. Ansaldo, BE; H. P. Soyer, MD, FACD; unpublished data; May 2013). Our microbiopsy device is 0.50 mm wide and 0.15 mm thick and results in a 0.21 ± 0.04-mm-wide puncture site in volunteer skin as measured using reflectance confocal microscopy. In a research letter in this issue of *JAMA Dermatology*, we have demonstrated the minimal impact that the choice of microbiopsy site has on the histopathologic diagnosis of a given melanocytic proliferation. The size of microbiopsy defects measured in this study was comparable to those of other artifacts more or less commonly seen in routine sectioned specimens, and the inherent diagnostic difficulties for the dermatopathologist encountered with the histopathologic assessment of a microbiopsied melanocytic skin lesion can easily be overcome by ordering of multiple levels.

**Synopsis and Utopia**

Microbiopsy devices have already been developed for breast and intestinal tissue on the basis of the step change advances in micromanufacturing and in molecular and genetic testing. The ingenious outcomes are meaningful analyses that can be obtained nowadays even from a few cells. We foresee that microbiopsies will become a feasible molecular sampling option for biobanking of equivocal melanocytic proliferations, and because of the simplicity of the sampling procedure, a multitude of melanocytic lesions can be biobanked easily in due course. In addition, the use of these samples can be maximized with nucleic acid amplification followed by whole genome and transcriptome sequencing that will be made open source, thereby creating a sort of virtual biobank in the cloud in the spirit of the ubiquitous big data concept. If only 1 or a few expert laboratories in collaboration with a few melanoma centers does this, our patients will benefit through open source data analysis linking the microbiome, virome, genome, transcriptome, and the noncoding RNA world with the clinical and dermoscopic phenotypes. Such an approach will probably change our understanding of the enigmatic and so often fateful nature of melanocytic proliferations to the better. One possible outcome may be a molecular profile assigned to a specific dermoscopic morphology, ie, a molecular imaging profile, that could give us insight into the molecular pathologic characteristics of a lesion using just dermoscopy imaging. Biobanking of melanomas and equivocal melanocytic proliferations will lose its research status soon and become a standard of care in dermato-oncology as an integral part of personalized medicine.

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**ARTICLE INFORMATION**

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