Re-excision of Moderately Dysplastic Nevi: Should we or shouldn’t we?

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Conflicts of Interest:

• NONE
Figure 1.
Clinical features of atypical nevi. Indistinct borders are evident in lesions (A), (B), and (C). Variable pigmentation is seen in these lesions as well as lesions (D), (E), and (F). Irregular borders are present in many of these lesions.
Fundamental questions:

• Why does this matter?
• What is a moderately dysplastic nevus?
• Are dysplastic nevi pre-malignant?
• Should margin status on biopsy impact our decision to re-excise a nevus?
• What is the most rational approach to managing dysplastic nevi given our current knowledge?
Fundamental questions:

• **Why does this matter?**
• What is a moderately dysplastic nevus?
• Are dysplastic nevi pre-malignant?
• Should margin status on biopsy impact our decision to re-excise a nevus?
• What is the most rational approach to managing dysplastic nevi given our current knowledge?
Why do we care about dysplastic nevi?
Clinical considerations:

• What is best for our patients?
• What is the cost of over-excising?
• What is the liability for under-excising?
Fundamental questions:

• Why does this matter?
• **What is a moderately dysplastic nevus?**
• Are dysplastic nevi pre-malignant?
• Should margin status on biopsy impact the decision to re-excise?
• What is the most rational approach to managing dysplastic nevi given our current knowledge?
Concept of dysplastic nevus

• 1978- Clark and colleagues – B-K mole syndrome

• 1978 – Lynch and colleagues – FAMMM Syndrome

• 1980 – Elder, Clark and colleagues – DNS
Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions

'The B-K Mole Syndrome'

Wallace H. Clark, Jr, MD; Ronald R. Reimer, MD; Mark Greene, MD; Ann M. Ainsworth, MD; Michael J. Mastrangelo, MD
Histology of B-K moles:

- Dermal component “like that of common nevi”

- “Atypical melanocytic hyperplasia” of junctional component
  - Synonymous with “melanocytic dysplasia”

- Individual melanocytes or small clusters of melanocytes “have some of the structural features of malignant melanocytes”
Fig 7.—Histology of B-K mole removed from patient illustrated in Fig 2 and 3. Both kinds of histological elements of B-K mole are illustrated. Nevic tissue is on left, and combination of atypical melanocytic hyperplasia, fibroplasia of papillary dermis, and lymphocytic infiltration is in right two thirds of photomicrograph. Proband, family M (hematoxylin-eosin, × 76).

Fig 6.—Nevic tissue on right in B-K mole and atypical melanocytes, fibroplasia, and lymphocytic infiltration on left. Patient was 24-year-old woman with B-K mole syndrome, but without malignant melanoma. Sister of proband of family M, whose various lesions are illustrated in Fig 2, 3, 7, 9, and 10 (hematoxylin-eosin, × 152).
Fig 9.—Atypical melanocytic hyperplasia at dermoepidermal interface. Higher magnification of area near right margin of Fig 7 (hematoxylin-eosin, × 608).

Fig 10.—Atypical melanocytic hyperplasia with three atypical melanocytes in dermis immediately deep to epidermis. Area is higher magnification of extreme right edge of Fig 7 (hematoxylin-eosin, × 608).
Concept emerges:

• Nevus > dysplastic nevus > melanoma in-situ/invasive melanoma

• “Precisely analogous to cervical dysplasia and senile keratosis: foci of squamous cells have some of the structural features of malignancy, but may remain indolent, regress completely, or progress to obvious carcinoma”

• Cervical dysplasia:
  • Mild dysplasia > moderate dysplasia > severe dysplasia > in-situ Ca>invasive Ca
Fig 12.—Histology of small flesh-colored nodule illustrated in lower portion of Fig 6, inset. Nevus component of B-K mole that gave rise to malignant melanoma as illustrated in Fig 5 and 6. Histology of melanoma arising in this lesion is shown in Fig 13 and 14. Proband, family G (hematoxylin-eosin, × 61).
Familial Atypical Multiple Mole- Melanoma Syndrome

• Reported 1978 by Lynch and colleagues
• Clinical paper - pedigree
• One family, 4 generations
• 4 family members with multiple melanomas in 2 generations
  • 3 of these had the atypical mole phenotype
  • 1 family member with the atypical mole phenotype did not have MM
• Several family members with > 200 nevi, some atypical (up to 3 cm)
• One patient had moles removed which were “atypical on histology”
• They propose it is same syndrome as “B-K Syndrome”

*Journal of Medical Genetics, 1978, 15, 352-356*
Dysplastic Nevus Syndrome:
A Phenotypic Association of Sporadic Cutaneous Melanoma

DAVID E. ELDER, MB, CHB,* LEONARD I. GOLDMAN, MD,† SUSAN C. GOLDMAN,† MARK H. GREENE, MD,‡ AND WALLACE H. CLARK, JR., MD*

Clinical photographs of 79 prospectively studied cases of non-familial cutaneous malignant melanoma were reviewed; special attention was directed to the distribution pattern of coexistent melanocytic lesions. A group of 15 patients had moles on the covered buttock area. Seven of these patients had large clinically atypical nevi, and biopsies of these nevi showed severe melanocytic dysplasia. Residual elements of melanocytic dysplasia were identified in five of the primary melanomas in this group of patients. It is suggested that these patients represent a distinctive syndrome, the Dysplastic Nevus Syndrome (DNS) and that they are at increased risk for development of primary cutaneous malignant melanoma. The clinically and histologically distinctive dysplastic nevi of these patients are identical to the precursor lesion for melanoma that we have previously described in a familial context, the B-K mole syndrome. This paper represents the first description of this form of dysplasia in non-familial melanoma.

Clinical Data on DNS patients

- Retrospective cohort of 79 patients with sporadic melanoma
  - All were followed in pigmented lesion clinic and had full body photography
- DNS Patients:
  - 7/79 patients has larger buttock nevi (0.5 – 1.5 cm)
- Avg number of nevi was 26 – mostly on back; variable pigmentation
- 13 clinically atypical pigmented lesions (other than their presenting MM) were biopsied in these 7 patients
  - 1 was a 2\textsuperscript{nd} melanoma
  - 3 were typical benign nevi
  - 9 were “dysplastic nevi”
Propose two classes of “dysplastic nevi”:

<table>
<thead>
<tr>
<th>Table 3. Histologic Features of Dysplastic Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common characteristics</strong></td>
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<tr>
<td>Nuclear pleomorphism and hyperchromatism</td>
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<tr>
<td>Lymphocytic inflammatory response with fibroplasia</td>
</tr>
<tr>
<td><strong>Epithelioid-cell dysplasia</strong></td>
</tr>
<tr>
<td>Epithelioid cells with dusty pigment</td>
</tr>
<tr>
<td>Nucleoli may be prominent</td>
</tr>
<tr>
<td>Lateral fusion and pleomorphism of nests</td>
</tr>
<tr>
<td>Small hyperchromatic nevus cells in papillary dermis</td>
</tr>
<tr>
<td><strong>Lentiginous melanocytic dysplasia</strong></td>
</tr>
<tr>
<td>Prominent cytoplasmic retraction artifact</td>
</tr>
<tr>
<td>Irregular (non-nested) basal melanocytic growth</td>
</tr>
<tr>
<td>Frequently junctional (no dermal component)</td>
</tr>
</tbody>
</table>
Features of “dysplastic nevi”

• “intraepidermal melanocytic dysplasia”
  • Nuclear pleomorphism or hyperchromatism in few or many cells

• Focal or diffuse lymphocytic filtrate with delicate fibroplasia and new vessel formation

• Lamellar fibroplasia, a condensation of collagen about elongated rete ridges with hyperplastic melanocytes, was commonly present
DNS concept (continued)

• Authors proposed that DN are precursors to melanoma based on the following:
  • Some patients with sporadic melanoma have “dysplastic nevi”
  • Some melanomas have “lentiginous melanocytic dysplasia” at the edge which may be evidence of a precursor “dysplastic nevus”
  • One patient with B-K Mole syndrome who was followed longitudinally developed a melanoma in a previously stable “dysplastic nevus”
FIG. 4A. Vertical growth phase (invasive nodule, left of field) in a superficial spreading melanoma from the same patient. The tumor fills and expands the papillary dermis (Level III) (×66). B. Peripheral portion of same lesion. Note basal proliferation of pleomorphic hyperchromatic melanocytes with prominent retraction artifact. Previously classified as a variant pattern of SSM, this appearance may represent residual element of a precursor lesion (lentiginous melanocytic dysplasia) (×250).
Defining “Dysplasia” as pertains to nevi:

- In 1984 Clark and colleagues wrote to try to better define dysplasia

- “The sine qua non of melanocytic dysplasia remains melanocytic nuclear atypia”

- “nuclear atypia” was never defined
Defining “Dysplastic Nevi” – W.H.O.

- 1991
- 6 dermatopathologists
- Reviewed published “criteria”
- Decide that atypia is a must for diagnosis of DN
- Defined atypia of melanocytes as “unlike the familiar appearance of normal melanocytes”

Major Criteria for DN (both required):

- Basilar proliferation of atypical nevomelanocytes
  - If there is a dermal component, basilar proliferation extends at least 3 rete beyond it
- Atypical intraepidermal prolif is a lentiginous or epithelioid pattern
WHO Criteria for DN (cont.)

• Minor criteria (at least 2):
  • Concentric eosinophilic fibrosis or lamellar fibroplasia
  • Neovascularization
  • Dermal inflammatory response
  • Fusion of rete ridges
Concordance rate for whether a lesion was a dysplastic nevus or not:

• Mean percent concordance = 88%

Figure 2.
Histologic features of dysplastic nevi. (A) Architectural disorder demonstrated by lateral asymmetry and “shouldering” (original magnification x40). (B) Lentiginous melanocytic hyperplasia with bridging of rete ridges (original magnification x200) and (C) cellular atypia (original magnification x200). (D) Patchy lymphocytic host response (original magnification x100). (E) Prominent eosinophilic fibroplasias (original magnification x200). (F) Variable and “random” cytologic atypia and mitotic junctional activity (original magnification x600).
Do we have a definition of DN?

• Have a proposal for features seen in DN

• Must be some component of “atypia” of melanocytes
  • “atypia” undefined, subjective

• Allows a group of pathologists to mostly agree if a given lesion is a “dysplastic nevus” or not
  • Room for improvement
NIH Consensus Conference

Diagnosis and Treatment of Early Melanoma

NIH Consensus Development Panel on Early Melanoma

THE INCIDENCE of melanoma of the skin appears to be rapidly rising. The increased incidence may be partially attributable to increased detection resulting from screening. In 1992, approximately 32,000 newly diagnosed cases and 7,000 deaths are expected in the United States. Melanoma tends to occur in adults in the prime of their family and professional lives. Detection and surgical treatment of the early stages of this malignancy are usually curative. In contrast, diagnosis and treatment in late stages often have dismal results.

Traits associated with an increased risk of developing melanoma include multiple typical moles, atypical moles, freckling, history of severe sunburn, ease of burning, inability to tan, and light hair with blue eyes. Other factors include the presence of familial atypical mole and melanoma syndrome, disorders of DNA repair, and excessive sun exposure.

Efforts to increase public awareness of melanoma and its treatment without causing unnecessary fear present a challenge. Public and professional education campaigns that emphasize sun protection and periodic total skin examinations for early detection of melanoma have the potential to save lives.

To resolve questions relating to the diagnosis and treatment of early melanoma, the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference from January 27 through 29, 1992.

After 2 days of presentations by experts and discussion by the audience, a consensus panel drawn from the specialties of dermatology, cutaneous pathology, surgery, internal medicine, and radiation oncology reached the following conclusions:

1. What are the clinical and histological characteristics of early melanoma?

Clinical Features.—Cutaneous melanoma is a distinctive and histological entity. Clinical features of de novo, premalignant lesions suggestive of melanoma include Asymmetry, Border irregularity, Color variegation, and Diameter greater than 6 mm (the ABCD's of melanoma). An asymmetry is one that is not regularly round or oval. Border irregularity refers to notching, scalloping, or poorly defined lesion margins. Color variegation refers to a lesion with shades of tan, red, white, or blue/black, or combinations thereof. Although a high level of suspicion exists for a lesion greater than 6 mm in diameter, early melanomas may be diagnosed in a smaller size. Earliest lesions are flat or macular and may have altered skin markings. However, a palpable lesion with a firm or irregular surface features or benign-appearing and nonpigmented lesions that change rapidly represent early melanoma.

Melanoma has classically been divided into subtypes:

- Superficial spreading melanoma (SSM) is the most common subtype, located on any anatomic site, and with
Members of the Consensus Development Panel were:

Lowell A. Goldsmith, MD, Conference and Panel Chairperson, Professor and Chair, Department of Dermatology, University of Rochester School of Medicine, Rochester, NY
Frederic B. Askin, MD, Professor of Pathology, Director of Surgical Pathology, The Johns Hopkins Hospital, Baltimore, Md
Alfred E. Chang, MD, Associate Professor of Surgery, Chief, Division of Surgical Oncology, University of Michigan, Ann Arbor
Cynthia Cohen, MB, BCh, Professor of Pathology, Director, Surgical Pathology, Department of Anatomic Pathology, Emory University School of Medicine, Atlanta, Ga
Janice P. Dutcher, MD, Associate Professor of Medicine, Department of Oncology, Albert Einstein Cancer Center, Montefiore Medical Center, Bronx, NY
Robert S. Gilgor, MD, Clinical Associate Professor of Dermatology, Duke University, Durham, NC, Clinical Professor of Dermatology, University of North Carolina at Chapel Hill, Private Practice, Chapel Hill, NC
Stephanie Green, PhD, Associate Member, Fred Hutchinson Cancer Research Center, Research Associate Professor, University of Washington, Seattle
Emily L. Harris, PhD, MPH, Assistant Professor, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Md
Stephen Havas, MD, MPH, MS, Associate Professor, Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore
June K. Robinson, MD, Professor of Dermatology and Surgery, Department of Dermatology, Northwestern University Medical School, Chicago, Ill
Neil A. Swanson, MD, Professor of Dermatology and Otolaryngology—Head and Neck Surgery, Head, Section of Dermatologic Surgery and Oncology, Oregon Health Sciences University, Portland
Margaret A. Tempero, MD, Associate Professor of Medicine, Section of Oncology/Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha

Speakers were:

A. Bernard Ackerman, MD: “Critique of Report” and “ Dysplastic Nevii”
Charles M. Balch, MD: “Diagnosis and Treatment of Early Melanoma”
Natale Cascinelli, MD (presentation given by Charles M. Balch): “One Centimeter Free Margins Excision is the Treatment of Choice for Patients With Stage I Melanoma Not Thinner Than Two Millimeters”
Wallace H. Clark, MD: “Workshop Without Walls Report”
Evan R. Farmer, MD: “Summary of Workshop Without Walls Report”
DuPont Guerry IV, MD: “Tumor Progression in Melanocytic Neoplasia: Lessons for the Clinic”
Alan N. Houghton, MD: “Prevention of Melanoma—A Realistic Goal”
Howard K. Koh, MD: “Population Screening and Education for Melanoma”
Alfred W. Kopf, MD: “What Is Early Melanoma”
Kenneth H. Kraemer, MD: “Genetics/Host Factors, UV”
Rona M. MacKie, MD, FRCP, FRCPath, FRSE: “Educational Activities Aimed at Earlier Diagnosis of Malignant Melanoma and Their Evaluation”
John C. Maize, MD: “Regression Melanoma”
Douglas A. Perednia, MD: “Developing Uses for Digital Imaging in the Diagnosis and Treatment of Melanoma”
Speakers at NIH Consensus Conference (cont)

Michael W. Piepkorn, MD, PhD: “Problems in Histologic Diagnosis of the Dysplastic Nevus”
Darrell S. Rigel, MD, MS: “Dysplastic Nevus Syndrome—Clinical Significance”
Gary S. Rogers, MD: “Follow-up Studies: Second Primary Melanoma”
Richard W. Sagebiel, MD: “A Mole by Any Other Name . . . the Presence of Precursor Moles in Association With Primary Malignant Melanoma”
Arthur J. Sober, MD: “Clinical Studies—Overview”
Margaret A. Tucker, MD: “Risk of Melanoma in Members of Melanoma-Prone Families”
Mary R. Wick, MD: “Overview of Histopathology”
John J. Zone, MD: “Family Studies of Malignant Melanoma and Dysplastic Nevus Syndrome.”
NIH Consensus Conference

• Recommended “dysplastic nevus” not be used
  • propose “nevus with architectural disorder” (NAD)

• Histological Criteria for NAD:
  • Asymmetry
  • Subepidermal fibroplasia: concentric, lamellar
  • “Lentiginous melanocytic hyperplasia” with spindle or epithelioid mcts
  • Nests vary in size
  • Nests fuse or “bridge” adjacent rete
  • Variable lymphocytic infiltration of dermis
  • “Shouldering” – extension of single or nested melanocytes beyond the main dermal component
NIH consensus conference 1992:

• Recommendation that pathologists report on the degree of melanocyte atypia
  • mild, moderate, severe

• No definition of mild/mod/severe atypia given

• Birth of the concept of “grading” of atypia
“It is strongly recommended and essential that dermatologists, pathologists, and dermatopathologists formulate a reproducible schema for diagnosing and reporting these nevi.”
Critical Analysis of Histologic Criteria for Grading Atypical (Dysplastic) Melanocytic Nevi

Lucia Pozo, MD, 1 Mahmoud Naase, PhD, 2 Rino Cerio, MD, 1, 2 Alfredo Blanes, MD, 3 and Salvador J. Diaz-Cano, MD 2

Key Words: Melanocytic nevus; Histologic grading; Severe dysplasia; Regression; Atypical-mole syndrome

Am J Clin Pathol 2001;115:194-204
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<td>4 (3.2)</td>
<td>9 (7.3)</td>
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**Figure 2** Diagnostic algorithm for grading atypical melanocytic nevi (AMN). Numbers represent the probability of finding that feature in low-grade AMN. The diagnostic accuracy dramatically improves if several histologic criteria are fulfilled.
FIRST DAY OF SUMMER VACATION!

PLAYS VIDEO GAMES WITH JEFFY.

MOMMY, THERE'S NOTHIN' TO DO.

MAKES A FEW DRAWINGS.

WALKS FENCE.

CLIMBS TREE.

HELPs FIX CAR's ENGINE.

WRESTLES BArFY.

CLIMBS MOUNTAIN.

JOINS BALL GAME.

Rides SKATEBOARD.

Wades IN RJ's POOL.

LISTENS TO MUSIC.

VISITS CLUBHOUSE.
Even if we can’t concisely define a moderately dysplastic nevus, can we still reliably recognize it?
“... I know it when I see it ...”

Supreme Court Justice Potter Stewart

(Jacobellis v. Ohio, 1964)
Interobserver agreement
Study 1
Histopathologic Recognition and Grading of Dysplastic Melanocytic Nevi: An Interobserver Agreement Study

Lyn M. Duncan, Marianne Berwick, Jan A. Bruijn, H. Randolph Byers, Martin C. Mihm and Raymond L. Barnhill

• “...if melanoma risk is related to degree of cytologic atypia in dysplastic nevi, dermatopathologists must be able to reliably distinguish two or more grades of melanocytic atypia in dysplastic nevi.”

Duncan, L et al. J Invest Dermatol; 100: 318S
Table II. Agreement in Diagnosis of Melanocytic Proliferations

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<th>Overall</th>
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<td>All nevi (including dysplastic nevi)</td>
<td>90%</td>
<td>84-94%</td>
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<td>versus melanoma</td>
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<td>(0.84-0.94)</td>
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<td>Nevi versus dysplastic nevi</td>
<td>77%</td>
<td>69-80%</td>
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<td>versus melanoma</td>
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<td>Dysplastic nevi slight</td>
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<td>versus moderate</td>
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<td>versus severe cytologic atypia</td>
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</table>

aData for concordance are expressed as percentages. The range of kappa statistic is listed below in parentheses.
Table I. Diagnosis by Observer$^a$

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Final</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign nevi (including those with 20 features of dysplasia)</td>
<td>20</td>
<td>23</td>
<td>20</td>
<td>29</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Dysplastic nevi (total)</td>
<td>30</td>
<td>25</td>
<td>30</td>
<td>20</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Slight atypia</td>
<td>10</td>
<td>14</td>
<td>11</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Moderate atypia</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Severe atypia</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>10</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

$^a$Number of cases diagnosed in each category by observers A-E; “Final” designates the reported diagnosis. Benign nevi include common nevi and nevi with some features, either cytologic or architectural, of dysplastic nevi but not fulfilling all of the criteria.
The advantage of a three-grade scale over a two-grade scale may be the allowance of a middle ground for cases where the degree of atypia is not obviously slight or severe. In fact, both of the less experienced observers appeared to use this "safe haven" and graded a disproportionate number of dysplastic nevi as moderate (Table I).
Interobserver agreement
Study 2
Table 2. Comparison of three-panel member’s independent reviews and final consensus interpretations according to MPATH-Dx diagnostic class (n = 201)

<table>
<thead>
<tr>
<th>Interpretations from independent reviews</th>
<th>Nevus/mild atypia, n = 22</th>
<th>Moderate atypia, n = 33</th>
<th>Severe atypia/melanoma in situ, n = 55</th>
<th>T1a melanoma, n = 42</th>
<th>T1b melanoma, n = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Nevus/mild atypia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 of 3 pathologists agreed</td>
<td>0</td>
<td>15 (45)</td>
<td>53 (96)</td>
<td>42 (100)</td>
<td>49 (100)</td>
</tr>
<tr>
<td>1 of 3 pathologists agreed</td>
<td>5 (5)</td>
<td>15 (45)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 of 3 pathologists agreed</td>
<td>8 (36)</td>
<td>3 (9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All 3 pathologists agreed</td>
<td>13 (59)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate atypia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 of 3 pathologists agreed</td>
<td>16 (73)</td>
<td>2 (6)</td>
<td>35 (64)</td>
<td>41 (98)</td>
<td>49 (100)</td>
</tr>
<tr>
<td>1 of 3 pathologists agreed</td>
<td>5 (23)</td>
<td>10 (30)</td>
<td>15 (27)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>2 of 3 pathologists agreed</td>
<td>1 (5)</td>
<td>16 (48)</td>
<td>5 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All 3 pathologists agreed</td>
<td>0</td>
<td>5 (15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe atypia/melanoma in situ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 of 3 pathologists agreed</td>
<td>19 (86)</td>
<td>16 (48)</td>
<td>1 (2)</td>
<td>24 (57)</td>
<td>48 (98)</td>
</tr>
<tr>
<td>1 of 3 pathologists agreed</td>
<td>3 (14)</td>
<td>13 (39)</td>
<td>8 (15)</td>
<td>13 (31)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2 of 3 pathologists agreed</td>
<td>0</td>
<td>4 (12)</td>
<td>21 (38)</td>
<td>5 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>All 3 pathologists agreed</td>
<td>0</td>
<td>0</td>
<td>25 (45)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T1a melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ok...But that’s just those dermpaths.

My dermpath guy/gal, they really know what they’re doing...
Pathologists’ diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

Joann G Elmore,1 Raymond I Barnhill,2 David E Elder,3 Gary M Longton,4 Margaret S Pepe,4 Lisa M Reisch,1 Patricia A Carney,5 Linda J Titus,6 Heidi D Nelson,7,8 Tracy Onega,9,10 Anna N A Tosteson,11 Martin A Weinstock,12,13 Stevan R Knezevich,14 Michael W Piepkorn15,16

BMJ 2017; 357:j2813
Study Design

• 187 pathologists in USA with at least one of 3 qualifications:
  • Fellowship trained or boarded in dermpath
  • Recognized by colleagues as expert in melanocytic proliferations
  • >10% of usual workload cutaneous melanocytic lesions

• 240 cases which had consensus diagnosis by 3 expert dermpaths were divided into 5 sets of 48

• Viewed same set of 48 slides twice - 8 months apart

• 36-39 pathologists viewed each set
  • Each group of pathologists was balanced for the 3 qualifications above
How well pathologists agree with *their own* diagnosis:

Table 3 | Intraobserver concordance of 118 pathologists’ interpretations of melanocytic skin biopsy lesions of the same case at phase 1 and phase 2 at least eight months apart*

<table>
<thead>
<tr>
<th>Phase 1 diagnosis</th>
<th>Phase 2 diagnosis (No of paired interpretations)</th>
<th>Intraobserver concordance† % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class I</td>
<td>Class II</td>
</tr>
<tr>
<td>Class I</td>
<td>1155</td>
<td>188</td>
</tr>
<tr>
<td>Class II</td>
<td>170</td>
<td>227</td>
</tr>
<tr>
<td>Class III</td>
<td>91</td>
<td>120</td>
</tr>
<tr>
<td>Class IV</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>Class V</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>1450</td>
<td>588</td>
</tr>
</tbody>
</table>

*Mean of Kappa statistic was calculated for each pair of interpreters.*
How well pathologists agree with a “standard diagnosis”:

Table 4 | Interobserver concordance of pathologists’ interpretations of melanocytic skin biopsy lesions. Pairwise comparison of interpretations by 187 participating pathologists in phase 1. Diagnoses for all possible ordered pairs of participants reading the same glass slide are included*

<table>
<thead>
<tr>
<th>First pathologist's interpretation</th>
<th>Second pathologist's interpretation</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
<th>Class V</th>
<th>Total</th>
<th>Interobserver concordance % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>64 122</td>
<td>15 082</td>
<td>11 223</td>
<td>2993</td>
<td>1773</td>
<td>95 193</td>
<td></td>
<td>71 (69 to 73)</td>
</tr>
<tr>
<td>Class II</td>
<td>15 082</td>
<td>10 366</td>
<td>11 028</td>
<td>3974</td>
<td>1903</td>
<td>42 353</td>
<td></td>
<td>25 (22 to 27)</td>
</tr>
<tr>
<td>Class III</td>
<td>11 223</td>
<td>11 028</td>
<td>31 326</td>
<td>12 675</td>
<td>4494</td>
<td>70 746</td>
<td></td>
<td>45 (42 to 47)</td>
</tr>
<tr>
<td>Class IV</td>
<td>2993</td>
<td>3974</td>
<td>12 675</td>
<td>22 334</td>
<td>8854</td>
<td>50 830</td>
<td></td>
<td>46 (43 to 49)</td>
</tr>
<tr>
<td>Class V</td>
<td>1773</td>
<td>1903</td>
<td>4494</td>
<td>8854</td>
<td>50 926</td>
<td>67 950</td>
<td></td>
<td>77 (75 to 79)</td>
</tr>
<tr>
<td>Total</td>
<td>95 193</td>
<td>42 353</td>
<td>70 746</td>
<td>50 830</td>
<td>67 950</td>
<td>327 072</td>
<td></td>
<td>55† (53 to 56)</td>
</tr>
</tbody>
</table>
“This low level of diagnostic precision is of clinical concern. ...the findings reported here are more pronounced than in other disciplines of medicine.”
Conclusions:

• Dysplastic nevus remains a poorly defined entity

• Grading of Moderate Atypia in Dysplastic Nevi is:
  • Poorly reproducible from pathologist to pathologist
  • Poorly reproducible *by the same pathologist at different time points*
  • More likely in the hands of less experienced pathologists
Fundamental questions:

- Why does this matter?
- What is a moderately dysplastic nevus?
- **Are dysplastic nevi pre-malignant?**
- Should margin status on biopsy impact our decision to re-excise a nevus?
- What is the most rational approach to managing dysplastic nevi given our current knowledge?
“The importance of grading dysplastic nevi rests on the notion that the biologic behavior of nevi at either end of the spectrum of dysplasia is different and that dysplastic nevi represent the middle ground in a continuum from benign common nevi to malignant melanoma.”

Duncan et al, J Invest Dermatol 1993(100): 318S-321S
Do DN progress to melanoma?

• Most atypical nevi in melanoma kindred patients remain stable or regress over 25 years \(^1\)

• Most melanomas develop *de novo* \(^1\)
  - Nevus-associated melanoma roughly equally split b/w DN and CN \(^2\)

• DN transplanted onto nude mice do not transform to melanoma spontaneously or with UV radiation \(^2\)

\(^1\)JAAD 2015; 73(3): 508 \(^2\)JAAD 2012; 67(1): 13
Are DN genetically distinct from common nevi?

Table 1. Molecular and genetic characteristics of dysplastic nevi compared with common nevi

<table>
<thead>
<tr>
<th>Molecular/genetic feature</th>
<th>DN compared with CN</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonality</td>
<td>Present in both</td>
<td>16,17</td>
</tr>
<tr>
<td>RNA expression patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitosis and apoptosis</td>
<td>Similar</td>
<td>16,18</td>
</tr>
<tr>
<td>Transcription regulation</td>
<td>Similar</td>
<td>16,19</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>Similar</td>
<td>20,21</td>
</tr>
<tr>
<td>p16 mutations</td>
<td>Rare in both</td>
<td>16,22</td>
</tr>
<tr>
<td>p53 protein expression</td>
<td>Increased in DN in 2 studies (similar in earlier studies)</td>
<td>16,23,24(16,25,26)</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1p and 9p deletions</td>
<td>Present in 17/60 DN but in none of the CN</td>
<td>16,27</td>
</tr>
<tr>
<td>9p21 deletions</td>
<td>Present in 12/22 DN and 2/20 CN</td>
<td>16,28</td>
</tr>
<tr>
<td>Proliferation (Ki-67)</td>
<td>Higher in DN</td>
<td>16,18,29</td>
</tr>
<tr>
<td>Reactive oxygen species</td>
<td>Elevated in DN compared with CN</td>
<td>16,30</td>
</tr>
<tr>
<td>Senescence markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF and IGFBP7</td>
<td>Similar rates in DN and CN</td>
<td>16,31</td>
</tr>
<tr>
<td>Dissociation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CN, Common nevus; DN, dysplastic nevus; IGFBP7, insulin growth factor binding protein 7.
Genomic Characterization of Dysplastic Nevi Unveils Implications for Diagnosis of Melanoma

Rachel D. Melamed¹,², Iraz T. Aydin³,⁴, Geena Susan Rajan³,⁴, Robert Phelps³,⁴, David N. Silvers⁵, Kevin J. Emmett¹, Georg Brunner⁶,⁷, Raul Rabadán¹,⁸ and Julide Tok Celebi³,⁴,⁸

Journal of Investigative Dermatology (2017) 137, 905–909;

• Looked at DN, congenital and Common Nevi is patients with the DNS phenotype

• Used NEXTGEN sequencing to look for number of mutations in nevi
Dysplastic Nevi
Common Nevi
Cong Nevi

Number of Mutations

Nonsynonymous  Synonymous

b
Fundamental questions:

• Why does this matter?
• What is a moderately dysplastic nevus?
• Are dysplastic nevi pre-malignant?
• **Should margin status on biopsy impact our decision to re-excise a nevus?**
• What is the most rational approach to managing dysplastic nevi given our current knowledge?
Should margin status on biopsy impact our decision to re-excise a nevus?

- Chicago derms survey: 89% would re-excise a mod dys nev with (+) margins
  - Only 9% would re-excise one with negative biopsy margins
- 2/3 of AAD survey respondents re-excise (J Am Acad Dermatol 2002;46:674-82)

What do margins on a shave bx mean?
- They DO NOT mean the lesion is out!
- (-) initial shave margins of NMSC $\rightarrow$ 25% have POSITIVE margins on deeper sectioning
  - Arch Pathol Lab Med. 2016;140:678–681
Background

• It is common practice to re-excite DN with margin involvement
  • 2/3 of AAD survey respondents re-excite (J Am Acad Dermatol 2002;46:674-82)

• Actual risk of progression to melanoma for DN is not known

• Multiple studies have sought to determine if observation of incompletely removed DN – especially Moderate DN – is safe
Observation of Mod DN with (+) margins:

• Study 1:
  • 115 DN (66 mild; 42 mod; 7 severe) which were within 0.2 mm of margin
  • Observed for mean of 17 years
  • No melanomas developed at site; no metastatic MM
    • (JAAD 2013; 68 (4):545-551)

• Study 2:
  • 55 atypical nevi, 29 which involved a margin, observed for at least 5 years (mean 6.2 years)
  • No melanomas arose in association with any of the previously bx’d nevi
    • Southern Medical Journal 2009; 102 (1): 45-48
Re-excision of Mod DN with (+) margins:

• Study 3:
  • 765 Mild and Moderate DN diagnosed 2010-2011 had (+) margins on bx
  • 495 were re-excised
  • 18% of re-excisions had residual nevus
  • 2/495 were upgraded to severely dysplastic nevus on re-excision
  • No melanomas were identified
    • JAAD 71(6): 1071-76

• Study 4:
  • 127 DN with (+) margins re-excised; 63 mild/mild-mod/or mod; 64 mod-sev/ sev
  • 2 re-excisions showed MIS; both were assoc with mod-severe lesions
    • JAMA Dermatol 2013;149(8):928-934.
Recurrence of moderately dysplastic nevi with positive histologic margins

Bryan Hiscox, MD, a Melissa R. Hardin, MD, b Ida F. Orengo, MD, a Theodore Rosen, MD, a Mohsin Mir, MD, a and A. Hafeez Diwan, MD, PhD a,b

Houston, Texas

Background: The Pigmented Lesion Subcommittee of the Melanoma Prevention Working Group recently published a consensus statement that incompletely excised moderately dysplastic nevi (MDN) without clinical residual pigmentation can be observed and not re-excised. However, data regarding recurrence of MDN with positive histologic margins are quite scant.

Objective: We sought to extend the reported findings with a study to determine the recurrence rate of MDN with positive histologic margins.

Methods: We performed a retrospective study on MDN with positive histologic margins that were not re-excised and for which at least 1 year of clinical follow-up was available.

Findings:

• “Moderately DN” with histologically involved margins recurred in ~4% of cases

• No melanomas arose during follow-up

• Conclusion:
  “Routine re-excision of moderately dysplastic nevi with positive histologic margins does not appear to be warranted.”
Dysplastic nevi with severe atypia: Long-term outcomes in patients with and without re-excision

Kathleen Engeln, MD, a Kaitlin Peters, MD, c Jonhan Ho, MD, MS, d Jaroslaw Jedrych, MD, d
Daniel Winger, MS, b Laura Korb Ferris, MD, PhD, c and Timothy Patton, DO c
San Diego, California and Pittsburgh, Pennsylvania

Background: Dysplastic nevi with severe atypia (severely dysplastic nevi [SDN]) are frequently re-excised because of the concern that these lesions may in fact represent early melanoma. Data on long-term follow-up of these patients are limited.

Objective: We sought to determine the rate of subsequent melanoma development in patients with SDN who underwent re-excision versus those who did not and to determine factors associated with decision to re-excite.

Methods: A retrospective single institutional study was conducted with 451 adult patients (mean age 41.3 years) with SDN biopsied between November 1994 and November 2004, with clinical follow-up of at least 5 years.

Results: In 451 patients with SDN, re-excision was performed on 36.6%. Two melanomas were diagnosed in the re-excision specimens. Subsequent metastatic melanoma developed in 7 patients, all of whom had a history of melanoma. Margin comments influenced decision to re-excite.
Fundamental questions:

- Why does this matter?
- What is a moderately dysplastic nevus?
- Are dysplastic nevi pre-malignant?
- Should margin status on biopsy impact our decision to re-excise a nevus?
- What is the most rational approach to managing dysplastic nevi given our current knowledge?
Consensus Statement

Addressing the Knowledge Gap in Clinical Recommendations for Management and Complete Excision of Clinically Atypical Nevi/Dysplastic Nevi Pigmented Lesion Subcommittee Consensus Statement

Caroline C. Kim, MD; Susan M. Swetter, MD; Clara Curiel-Lewandrowski, MD; James M. Grichnik, MD, PhD; Douglas Grossman, MD, PhD; Allan C. Halpern, MD; John M. Kirkwood, MD; Sancy A. Leachman, MD, PhD; Ashfaq A. Marghoob, MD; Michael E. Ming, MD, MSCE; Kelly C. Nelson, MD; Emir Veledar, PhD; Suraj S. Venna, MD; Suephy C. Chen, MD, MS

JAMA Dermatol 2015;151(2):212-218
Consensus of pigmented lesion sub-committee:

“Observation may be a reasonable option for management of moderately DN with positive histologic margins without clinically apparent residual pigmentation; however, more data are needed to make a definitive recommendation”
A prospective study evaluating the utility of a 2-mm biopsy margin for complete removal of histologically atypical (dysplastic) nevi

Vitaly Terushkin, MD, Elise Ng, MD, Jennifer A. Stein, MD, PhD, Susan Katz, MD, David E. Cohen, MD, Shane Mechan, MD, and David Polsky, MD, PhD

New York, New York

CAPSULE SUMMARY

- Biopsy sites of dysplastic nevi (DN) are frequently re-excised if margins are positive after the initial procedure.
- A saucerization biopsy with a 2-mm peripheral margin of normal skin completely removes nearly 9 of 10 DN.
- This technique may decrease second procedures at DN biopsy sites, thereby decreasing patient morbidity and saving health care dollars.
A nongrading histologic approach to Clark (dysplastic) nevi: A potential to decrease the excision rate

Daniel F. Lozeau, MD, Michele J. Farber, MD, and Jason B. Lee, MD

Philadelphia, Pennsylvania

(J Am Acad Dermatol 2016;74:68-74.)
Grading Atypia vs. Non-grading approach

**Grading:**
- Implies DN are intermediate between benign and malignant
- Potential for miscommunication regarding management
- Bx margin status reported on all
- Results in high rate of re-excision: 22-55%

**Non-Grading**
- States when a lesion defies clear categorization as B9 or malig
  - Clark’s nevus with atyp feat
- Clearly indicates when re-excision is warranted
- Margins only reported when excision recommended
- Lowers re-excision rate to 11%
Summary:

• DN remain controversial
• Diagnosis and management of DN has not been standardized
• Grading of atypia in these nevi is subjective and promotes overtreatment
• The non-grading approach, clear statements indicating when a lesion defies confident assignment to a benign diagnosis, results in fewer re-excisions
  • Re-excision rates higher than 10-15% are likely overtreatments
• Good saucerization technique with margins of 2mm reduces re-excisions while providing optimal specimens