# The tumor genetics of acral melanoma: What should a dermatologist know?

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Dermatologists stand at the gateway of individualization of classification, treatment, and outcomes of acral melanoma patients. The acral melanoma genetic landscape differs in vital ways from that of other cutaneous melanomas. These differences have important implications in understanding pathogenesis, treatment, and prognosis. The selection of molecularly targeted therapy must be adapted for acral melanoma. It is also critical to recognize that tumor development is far more complex than an isolated event, reliably treated by a medication acting on a single target. Tumors exhibit intratumor genetic heterogeneity, metastasis may have different genetic or epigenetic features than primary tumors, and tumor resistance may develop because of the activation of alternative genetic pathways. Microenvironmental, immune, and epigenetic events contribute and sustain tumors in complex ways. Treatment strategies with multiple targets are required to effectively disrupt the tumor ecosystem. This review attempts to translate the current molecular understanding of acral melanoma into digestible concepts relevant to the practice of dermatology. The focus is tumor genetics defining potentially treatable cancer pathways, contextualized within the relevant pathologic and molecular features. (JAAD Int 2020;1:135-47.)

***Key words:*** acral melanoma; dermatology; genetics; melanoma; molecular; oncology; tumor genetics.

## INTRODUCTION

Acral melanoma is a unique tumor within the melanoma spectrum. Its molecular features are gradually being unraveled. Molecularly targeted therapies have revolutionized melanoma management by offering unprecedented responses in some patients. As such treatments become increasingly available, dermatologists should have a working understanding of these concepts. Melanoma classification will increasingly include, and likely be determined by, molecular findings. The molecular characteristics of acral melanoma will contribute to understanding its pathogenesis, enabling potentially preventive actions and therapies.

Vagaries and misconceptions have impaired our understanding of acral melanoma. Acral melanoma here refers specifically to melanoma on the palms, soles, and nail unit (sun-protected sites). Melanoma on the dorsal surface of the hands and feet should be grouped with other more common forms of

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cutaneous melanoma, frequently driven by ultraviolet (UV) radiation exposure.[1] Traditional classification systems of melanoma have resulted in the misconception that all acral melanomas are acral lentiginous melanomas. Although the most common histologic subtype, not all acral melanomas take the lentiginous form.[2,3] Many studies focus on acral lentiginous melanoma, omitting an important subgroup of acral melanoma. Whether subungual melanoma is a separate entity from other acral melanoma variants remains uncertain. A differentiation between melanomas arising from the nail matrix (initially linear melanonychia) and those arising on dorsal, sun-exposed skin of nail folds may be necessary.

**CAPSULE SUMMARY**

- The tumor genetics of acral melanoma are very different from those of ultraviolet radiation–induced melanoma, having different significantly mutated genes, lower mutational burdens, more structural variants, and fewer ultraviolet radiation–induced mutations.
- Clarification of acral melanoma subgroups on a clinical, pathologic, and molecular basis is necessary, but not yet complete.

A clear approach to the clinical, pathologic, and molecular subgrouping of acral melanomas will identify acral melanoma patients eligible for targeted therapies based on pharmacogenomic markers. Clarification of these acral melanoma subgroups is incomplete. This review presents an update on acral melanoma tumor genetics as it applies to the practice of dermatology. Clinical applications of this knowledge are presented together with a brief contextualization of tumor genetics within the larger tumor ecosystem. This overview first presents data to facilitate cursory reading about acral melanoma; second, more specific detail for specialized readers.

## TUMOR GENETICS OF ACRAL MELANOMA

### Relevant pathways in melanoma development

Tumorigenesis is a result of complex interactions between genetic changes in the tumor and the patient and environmental (including microenvironmental) factors.[4] Table I summarizes important cellular pathways in acral melanoma. Separation of these pathways gives the impression they are discrete, parallel processes; however, there are many interactions between them.

In acral melanoma, cancer pathways are activated in different ways from UV radiation–induced cutaneous melanoma. They interact with one another in complex ways. Inhibiting one pathway may result in deviation to and tumor stimulation via another. How aberration in specific pathways is more conducive to development of different acral melanoma subgroups, such as acral lentiginous melanoma, nodular acral melanoma, or nail melanoma, is unclear.

### Genetic changes observed in acral melanoma tumors

**Driver mutations.** Driver mutations vary significantly among melanoma subtypes.[23] Whole exome sequencing (analysis of the entire coding portion) of tumor DNA often leads to the identification of many mutations.[24] The identification of driver mutations leading to tumorigenesis (as opposed to passenger mutations) is challenging.[25] This is particularly problematic in cutaneous melanoma, in which the mutagenic effects of UV radiation result in a high mutational burden.[26,27] Many driver mutations are current or potential targets of molecular therapies. Acral melanomas have significantly lower mutational burdens than cutaneous melanomas.[26] It is unknown whether this applies to different subgroups and stages of acral melanoma. Driver mutations are more easily identified in acral melanoma because of their lower rate of somatic mutations.[28]

Intratumoral and intertumoral heterogeneity must also be considered. Analysis of a single clone of tumor cells may disregard important driver mutations in other tumor clones.[7,29,30] Molecular alterations leading to tumor progression and metastases are poorly understood.

The genomic classification of melanomas by the Cancer Genome Atlas identifies 4 subtypes of melanomas based on their driver mutations: *BRAF, RAS, NF1,* and the triple wild type.[31] These typically result in dysfunction of the mitogen-activated protein kinase pathway. Each group has distinct clinical and genetic features.[32] Approximately half (42%-55%) of acral melanomas studied to date have *BRAF, RAS,* or *NF1* mutations; the others fall into the triple-wild-type group.[22] *BRAF, NRAS,* and *NF1* alterations were mutually exclusive in 1 acral lentiginous melanoma study.[14] Subungual and interdigital melanomas display the most diverse driver mutations.[17]

Absence of *BRAF, RAS,* or *NF1* hot-spot mutations defines the triple-wild-type group (ie, all 3 "typical" melanoma mutations are wild type or normal).[31] Mitogen-activated protein kinase pathway activation still occurs in most triple-wild-type melanomas.[33] Triple-wild-type driver mutations are observed in 45% to 58% of acral melanoma cases.[22] These include

**Table I.** Cellular pathways with a pathogenetic role in acral melanoma

| Pathway | Cellular activity | Role in acral melanoma |
|---|---|---|
| MAPK[5] | Cellular proliferation, differentiation, and survival[6] | Activated in more than 90% of melanomas[7]<br>Stimulated by activating *BRAF* and *NRAS* mutations and inactivating *NF1* mutations[5]<br>Stimulated by upstream receptor tyrosine kinases (eg, *KIT*)[8]<br>Collateral effects allow tumor to evade immune system[5]<br>Constitutive activation of this pathway demonstrated in ALM (in situ and invasive) and the AM group as a whole[5,9] |
| *PI3K/AKT/PTEN*[5] | Permits cellular survival (antiapoptotic)[10] | *PTEN* antagonizes the *PI3K/AKT/mTOR* pathway, acts as a tumor suppressor[10]<br>Stimulated by upstream receptor tyrosine kinases (eg, *KIT*)[8] |
| *JAK/STAT3*[5] | Regulates cellular proliferation, differentiation, migration, and survival (context dependent)[11] | Regulates the PD-1 immune checkpoint, a mechanism of immune escape for melanomas[12]<br>May correlate with more advanced AM[5] |
| *TERT*[5] | Regulates telomere maintenance[13] | *TERT* activation essential in tumor development<br>Confers immortality to melanoma cells by maintaining telomere length[13]<br>Abnormally activated in 37% of AM patients in 1 study[14] |
| *CDK4/CDKN2A*[5] | Directs the cell cycle<br>*CDK4* = an oncogene<br>*CDKN2A* = a tumor suppressor gene that encodes *p16*<br>*RB1* and *p53* also involved in this pathway<br>Also stimulated by the MAPK pathway via cyclin D1[15] | *CDK4* exhibits rare germline mutations leading to melanoma, whereas germline CDKN2A mutations detected in 10%–25% of melanoma-prone families[16]<br>Nongermline aberrations also critical:<br>Activation in AM, especially in subungual/interdigital melanomas[17,18]<br>Pathway abnormally activated in 51% of AM patients in 1 study[14] |
| *MDM2/TP53*[5] | Determines senescence and apoptosis[14]<br>*P53* inhibited by *MDM*, supporting oncogenesis<br>*MDM* and *p53* interact in complex ways[19] | Abnormal activation identified in 17% of AM in 1 study[14] |
| *WNT* signaling[4] | Determines cellular proliferation, migration, polarity, and fate[4]<br>Interacts with *MITF*[20] | Exact role in melanoma unclear[21]<br>Mutated *CTNNB1* in an AM raises the possibility[21] |
| *MCR1-MITF* | Interaction between cellular activities such as melanin synthesis and the oncogene *MITF*, as well as the *CDK4/CDKN2A* pathway | Germline *MCR1* variants associated with increased melanoma risk in general[8]<br>A subtype of AM shows *MITF* aberrations[22] |

*ALM*, Acral lentiginous melanoma; *AM*, acral melanoma; *MAPK*, mitogen-activated protein kinase.

genetic alterations in a variety of genes, including *KIT, CCND1, CTNNB1, KDR (VEGFR2), MDM2, BCL2, AKT3, IDH1, GNAQ* (uveal melanoma), *GNAS, CDK4, CDKN2A, MITF, PTEN, RB1, TP53, APC, ERBB2, ERBB3, NUAK2, ABCB5,* and *TERT*.[3,22,26,31,34-39]

Deleterious *KIT* mutations or amplifications are frequently an early event in acral melanoma development (3%-36%), specifically directing lentiginous growth.[3,22,40] *KIT* mutations activate both the mitogen-activated protein kinase and *PI3K/AKT* pathways.[41] Most *KIT* mutations described in acral

melanoma are in exons 9, 11, 13, 17, and 18.[42,43] *PDGFRA* is often coamplified with KIT, although the converse is also reported.[3,36] It appears to be a critical event in acral melanoma.[3] *NF1* and *SPRED1* losses may occur with or without *KIT* driver mutations.[44]

*BRAF* variants play a smaller role in acral melanoma (10%-35% of cases).[12,22] Both typical V600E and other mutations (eg, V600L) are reported.[45] Alternative *BRAF* mutations to V600E occurred in 5% of cases in a recent study.[44] A molecular subclassification of acral melanoma based on *BRAF* mutation was proposed: acral melanoma with typical *BRAF* mutations observed in cutaneous melanoma, potentially responsive to BRAF inhibitors; and acral melanoma with non-*BRAF* mutations with other potentially actionable targets. This study also found that acral melanomas with *BRAF* mutations were less likely to be of the acral lentiginous melanoma subtype.

*NF1* driver mutations are observed in 11% to 23% of acral melanomas.[22] *NF1* is a tumor suppressor; therefore, alterations leading to loss of function of this gene need to arise on both chromosomes. *NF1* mutant tumors are generally associated with poor prognosis.[31,32] Homozygous *NF1* deletions were more common than point mutations in an acral lentiginous melanoma study.[14]

*RAS* genetic alterations are observed in 9% to 22% of cases.[12,22] *NRAS* mutations are at the same nucleotide positions as observed in cutaneous melanoma.[5]

Melanoma genetics studies tend to originate from a few centers, and it is uncertain whether their findings apply to other geographic regions and understudied population groups.[22] Lower prevalences of *KIT, NRAS,* and *BRAF* are reported in acral melanoma in some populations.[21] The main findings of acral melanoma cohorts sequenced to date are summarized in Table II.

**Mutational burden.** Because acral melanomas are not typically UV radiation induced, they have lower mutational burdens.[23,26] High tumor mutational burden theoretically improves responses to immunotherapies.[51] In practice, case series show similar efficacy in cutaneous melanoma and acral melanoma.[22]

**Mutational signatures.** In cutaneous melanoma, high levels of cytosine to thymine mutations are observed. These frequently show UV radiation mutational signatures not observed in acral melanoma, even if cytosine to thymine mutations are observed.[26] Mutational signatures in acral melanoma are different and are reported in other cancers, but not cutaneous melanoma.[23] Rates of non–cytosine to thymine mutations (guanine to adenine) are also lower in acral melanoma.[26] The presence of specific mutational signatures has prognostic implications in cutaneous melanoma.[52] Whether this extends to non-UV radiation signatures in acral melanoma is uncertain.

UV radiation signatures are identified in only a small proportion of acral melanoma.[14,50,53,54] In accordance with the relatively more frequent occurrence and worse prognosis of acral melanoma in people with darker Fitzpatrick skin types compared with that for other types of melanoma, authorities have justified the use of aggressive sun protection in this group. This approach is questionable because acral melanoma is not commonly associated with UV radiation–induced mutations.

UV radiation signatures in subungual melanomas are reported, whereas it has been shown that the nail plate blocks the majority of UV radiation.[22,53,55]

**Structural variants.** Structural variants represent genetic variation larger than 50 base pairs.[56] Acral melanoma shows a higher frequency of structural variants than cutaneous melanoma[23,57] because of entirely different mutational processes that occur in acral melanoma.[23,31] Subungual and interdigital melanomas have more copy number aberrations compared with both volar and dorsal melanomas of acral skin (*CDK4* and cyclin D1).[17] Copy number gains in *BIRC2, BIRC3,* and *BIRC5* (antiapoptosis genes) correlate with poor melanoma-specific survival.[37] Amplifications in *PAK1, GAB2,* and *IL7R* are identified in acral melanoma.[14,44,58] *ALK* break points occurred in 6.9% of acral melanomas in 1 study.[59] *CDKN2A* deletions are common (15.8%-35%).[14,23,35]

**Telomere length and pathway alterations.** Alterations in telomere length do not correlate with melanoma subtype.[23] An association was detected between short telomeres (and *TERT* aberrations) and poor melanoma survival.[22,60] Telomerase pathway alterations are reported in 9% to 45% of acral melanoma.[22] *TERT* promoter variants are less common in acral melanoma (9%-41%) than in cutaneous melanoma (more than 50%).[22] However, in 45% of acral melanoma with *TERT* aberrations, *TERT* copy number gains are noted (as opposed to point mutations typically observed in cutaneous melanoma).[22,61] A high frequency of *TERT* promoter mutations was reported in acral melanomas involving the digit and nail (38.8%).[1]

**Gene fusions.** Gene fusions occur when 2 previously independent genes are joined. When an upstream gene is turned on in the tumor cell, this can activate a downstream gene.[62] Kinase fusions activate the mitogen-activated protein kinase

**Table II.** Reported genetically sequenced acral melanoma cohorts (adapted from Chen et al[5])

| Study | Cases, no. | *KIT*, % | *BRAF*, % | *NF1*, % | *RAS*, % | Other |
|---|---|---|---|---|---|---|
| Curtin et al[46] 2005 (targeted sequencing) | 36 | Not sequenced | 23 | Not sequenced | 10 | Structural changes, amplifications in 89%; *CDK4* amplifications, *CDKN2A* losses more common than other CM |
| Krauthammer et al[28] 2012 | 17 (9 metastases) | 29.4 | 0 | 0 | 11.8 | 1 *RAC1* mutation<br>Copy gains in 5p13, 11q13 and 12q14 more common than other CM<br>3 *DYNCC1I1* mutations |
| Zebary et al[47] 2013 (targeted sequencing) | 88 ALMs | 15 | 17 | Not sequenced | 15 | 4% *PTEN* mutations (25 tumors sequenced) |
| Furney et al[26] 2014 | 5 (all metastases) | 40 | 40 | 0 | 0 | 0% *TERT* promoter mutations |
| Puntervoll et al[43] 2014 (targeted sequencing) | 36 (24 Tanzanian) | 11.1 | 11.1 | Not sequenced | 11.1 *NRAS* | — |
| De Lima Vazquez et al[48] 2016 (targeted sequencing) | 61 ALM | 20.7 | 10.3 | 0 | 7.5 *NRAS* | 9.3% *TERT* promoter mutations<br>*PDGFRA* mutation in 14.8% |
| Liang et al[14] 2017 | 34 ALM (17 metastases) | 2.6 | 18.4 (and 2.6 homozygous deletions) | 7.9 (loss/homozygous deletions) | 10.5 *NRAS*, 5.3 *KRAS* (and 2.6 amplifications) | 2.6% *TERT* promoter mutations<br>10.5% *TERT* amplifications<br>*PAK1* copy gains in 15% |
| Shim et al[21] 2017 | Composite of Asian cases reported | 10.2 (51/498) | 10.4 (40/383) | — | 6.6 *NRAS* (18/273) | — |
| Hayward et al[23] 2017 | 35 | 8.6 | 22.8 | 25.7 | 17.1<br>11 *NRAS* | Substantially more complex structural rearrangements<br>*CCND1* rearrangements |
| Kong et al[18] 2017 | 514 | — | — | — | — | 39.5% *CDK4* gain<br>26.7% *CCND1* gain<br>60.3% $P16^{INK4a}$ loss |

Continued

**Table II.** Cont'd

| Study | Cases, no. | *KIT*, % | *BRAF*, % | *NF1*, % | *RAS*, % | Other |
|---|---|---|---|---|---|---|
| Roh et al[49] 2017 | 46 | — | — | — | — | 10.9% *TERT* promoter mutations |
| Moon et al[35] 2018 | 64 | 10.9 | 34.4 | 17.2 | 21.9 *NRAS* | 17.2% *GNAQ* |
| Haugh et al[17] 2018 | 22 (9 volar, 13 nail unit/ interdigital) | 4.5 | 13.6 | 4.5 loss | 22.7 *NRAS* | 9.1% *TERT* gains<br>22.7% *CCND1* gains<br>13.6% *CDK4* gains<br>13.6% *PAK1* gains<br>18.2% *GAB2* gains |
| Gao et al[45] 2018 (targeted sequencing) | 40 | Not sequenced | 30 | Not sequenced | 10 *NRAS* | 7.5% *PTEN* mutations |
| Yeh et al[44] 2019 (targeted sequencing) | 122 | 11.5 (and 2.5 fusions) | 21.3 | 14.8 (inactivation) | 27.9 *NRAS* | 5.3% *TERT* promoter mutations<br>10.7% *TERT* amplifications<br>Amplifications in *PAK1* and *GAB2* (22.1%), *CDK4* (22.1%), and *CCND1* (19.7%), among others |
| Zaremba et al[1] 2019 | 50 (including dorsal lesions) | 6 (not clear whether it includes dorsal lesions) | 21.7 | 17.3 | 39.1 | 8.6% *TERT* promoter mutation |
| Sheen et al[37] 2019 | 45 | 24.4 | 8.9 | 11.0 | 26.7 *NRAS* and *KRAS* | 68.9% with cell cycle aberrations (*CDK4/6, CCND1/2, CDKN2A*)<br>35.6% with other receptor tyrosine kinase gains (eg, *EGFR*, *PDGFRA*)<br>33.3% with antiapoptosis gains (eg, *BIRC 2, 3, 5*) |
| Shi et al[50] 2019 | 29 | 13.8 | 27.6, 3.4 gains | 10.3 mutations | 10.3 *NRAS* | 10.3% *CDKN2A* mutations<br>17.2% *CDKN2A* losses<br>6.9% *TERT* promoter mutations<br>13.8% *TERT* copy number variants<br>6.9% fusions |

*ALM*, Acral lentiginous melanoma; *CM*, cutaneous melanoma; —, not available.

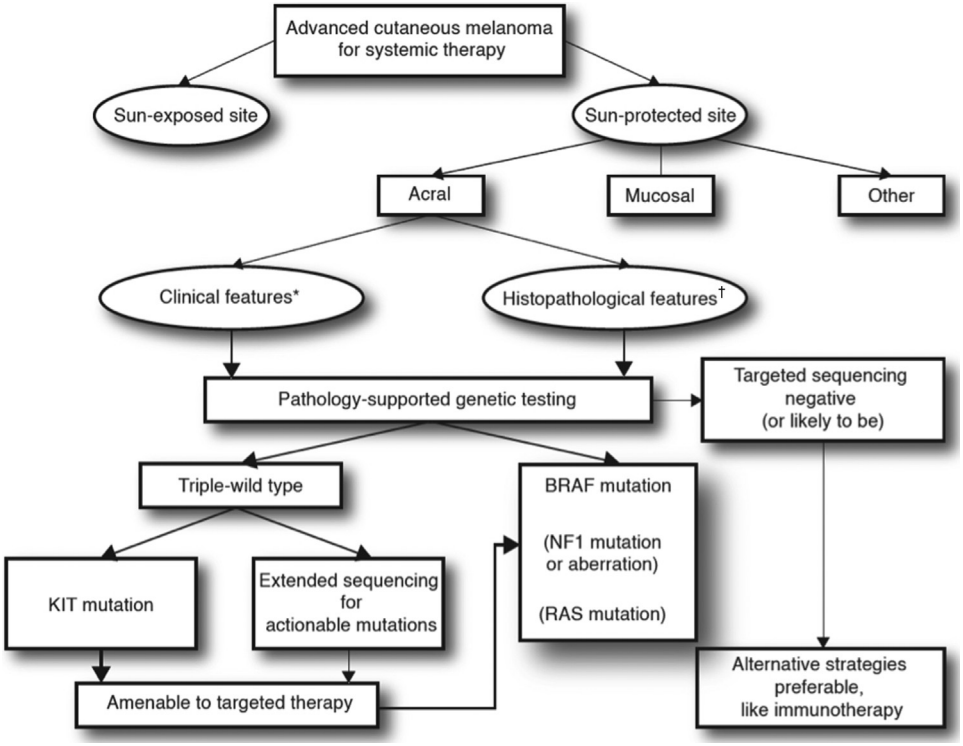


**Fig 1.** Acral melanoma: Projected algorithm for pathology-supported genetic testing, composing targeted sequencing based on clinical* and histopathologic† features referred to in Table III.

**Table III.** Clinical and histopathologic features (referred to in Fig 1) potentially helpful in predicting mutational status

| Clinical* and histopathologic features† | Associated mutation/alteration |
|---|---|
| Young (possibly <50 y) with ALM* | BRAF[72] |
| Female sex* | BRAF[47] |
| Nevus-associated AMs*† | BRAF[73] |
| ALM in general† | Non-BRAF[44] |
| Lentiginous growth pattern† | KIT[3] |
| Epithelioid cells† | BRAF mutation[35] |
| Bizarre cells† | NRAS, NF1 mutations[35] |
| Spindle cells with prominent dendrites† | NF1, GNAQ mutations[35] |
| Advanced Clark level (≈Breslow thickness)† | KIT[48] |
| Ulceration† | CDK4/6, CCND1/2, CDKN2A and receptor tyrosine kinase aberrations[18,37] |
| ALM with low mitotic rate† | TERT promoter mutations[48] |
| Amelanotic AM† | KIT aberrations[35,74] |

*ALM*, Acral lentiginous melanoma; *AM*, acral melanoma.
*Clinical.
†Histopathologic.

pathway in acral melanoma through mechanisms other than *BRAF, RAS,* or *KIT* mutations.[44] Kinase fusion genes seem to play a particular role in melanomas lacking common coding mutations (pan-negative melanoma, lacking *BRAF, NRAS, KRAS, HRAS, NF1, KIT, GNAQ,* and *GNA11*).[62] Kinase gene fusions reported in acral melanoma include *PAK1, DGKB, RET,* and *NTRK1*.[23,62] Receptor tyrosine kinase fusions were found in 4%, fusions of *BRAF* in 3%, and *protein kinase C* fusions in 1% of acral melanomas in a recent study.[44] These gene fusions present potentially actionable targets.[62]

## Intratumor heterogeneity

Intratumor heterogeneity is the morphologic and genetic variation of different clones of tumor cells

**Table IV.** Correlations between molecular lesions or activity, potential metastatic acral melanoma treatments, responses, and resistance mechanisms*

| Target | Treatments | Agents† | Responses‡ | Known resistance mechanisms‡ |
|---|---|---|---|---|
| Genetic pathway | | | | |
| MAPK | BRAF inhibitors§ (BRAF mutation) | Vemurafenib*<br>Dabrafenib mesylate*<br>Encorafenib* | ORR alone in AM 61.5%<br>Combination BRAF/MEK inhibition in AM up to 79%[5] | Intrinsic and acquired resistance<br>Development of new mutations, epigenetic and transcriptome alterations<br>Paradoxic reactivation of MAPK pathway<br>Upregulation of *PI3K* and *Ral* pathways[76] |
| | MEK inhibitors§ (BRAF mutation) | Trametinib*<br>Cobimetinib*<br>Binimetinib* | BRAF/MEK inhibition in AM up to 79%[5] | Upregulation of *PI3K* and *Ral* pathways[76] |
| | RTK inhibitors (KIT mutation) | Imatinib<br>Dasatinib<br>Nilotinib<br>Sunitinib | Response rates up to 27%[77] | Rapid development of resistance<br>Downstream activation of various kinases<br>Upregulation of receptor tyrosine kinases[78] |
| | ERK inhibitors | Ulixertinib<br>Ravoxertinib | Clinical trials[76] | |
| *PI3K/AKT/PTEN* | PI3K/Akt/mTOR inhibitors | Sirolimus (rapamycin)<br>Everolimus<br>AZD5363<br>LY294002 | Investigational[79] | |
| | RTK inhibitors | As above | | |
| *JAK/STAT3* | RTK inhibitors | May inhibit this pathway too[80] | | |
| *TERT* | TERT or telomerase inhibitors | EGCG | Investigational, no clinical trials on melanoma to date[81] | |
| *CDK4/CDKN2A* | CDK inhibitors | Abemaciclib<br>Palbociclib<br>Dinaciclib | Clinical trials[82] | |
| *MDM2/TP53* | MDM2/p53 Interaction inhibitors | AMG232<br>Actinomycin D | Clinical trials[83] | |
| *WNT* signaling | WNT modulators | LGK974 | Clinical trial[84] | |
| *MCR1-MITF* | P300/CBP inhibitors | A-485 | Investigational[85] | |

| | | | | |
|---|---|---|---|---|
| Immune system | | | | |
| Immunotherapies | Immune checkpoint inhibitors | Ipilimumab* | ORR with nivolumab or pembrolizumab in AM up to 32%[5] | Reduced TILs in AM<br>Reduced PD-L1 expression in AM<br>Lower somatic mutation rate in AM[5] |
| | | Nivolumab* | | |
| | | Pembrolizumab* | | |
| | Vaccine | Talimogene laherparepvec (t-vec)* | Durable RR 16.3%[86] | — |
| | Cytokine | IL-2 (high dose)* | ORR 16%[87] | — |

*AM*, Acral melanoma; *EGCG*, epigallocatechin-3-gallate; *IL-2*, interleukin-2; *MAPK*, mitogen-activated protein kinase; *ORR*, overall response rate; *RR*, response rate; *TIL*, tumor-invading lymphocyte.
*Food and Drug Administration approved for clinical use in melanoma.[88]
†Not an exhaustive list.
‡All melanoma subtypes, not exclusively acral melanoma (unless otherwise stated).
§Existing and proposed combination therapies may overcome resistance (eg, BRAF and MEK inhibitors, BRAF/MEK inhibitors and immune checkpoint inhibitors, MEK inhibitors, CDK inhibitors, PI3-Akt-mTOR inhibitors).

within a single tumor.[30] This is a possible mechanism for failure of targeted therapy, including the development of recurrences.[7] It was detected in acral melanoma during assessment of *BRAF* and *KIT* mutations.[7,63] It is an extensive and early event in acral melanoma development.[64] Thus, the concept of "treating a single mutation" is an oversimplification.

### Mutations in metastases and recurrences

Discordance has been reported between mutations detected in primary acral melanomas, their metastases, and recurrences (intrapatient intertumoral heterogeneity).[29,30] This phenomenon has important implications when targeted therapies are used and advocates for multimodal therapy in patients with advanced disease.

## CLINICAL APPLICATIONS OF TUMOR GENETICS

### Diagnosis

Fluorescence in situ hybridization can detect acral melanoma–specific genetic alterations to assist diagnosis of early or equivocal lesions. The analysis of genes such as *RREB1, CEP6, MYB,* and *CCND1* provides valuable ancillary information.[36,65,66] Single-nucleotide polymorphism arrays also provide a mechanism by detecting copy number changes in areas characteristic of melanoma.[67] Mutational analyses may identify the primary tumor site in metastatic disease with uncertain primary, as described in ocular melanoma, in which distinguishing between conjunctival, uveal, and cutaneous primaries is relevant to treatment and follow-up.[68]

### Excision margin assessment

*CCND1* amplifications are described in otherwise apparently normal melanocytes surrounding acral melanoma.[36] Isolated melanocytes showing gene amplifications may occur up to 3 mm from the histologic tumor-free surgical excision margin.[69]

### Classification: correlation between genotype and phenotype in acral melanoma

Clinical and pathologic features will be integrated to inform targeted sequencing of melanomas and identify suitable therapies. Extensive sequencing of tumors (whole exome or whole genome sequencing) is not practical, cost-effective, or easily interpreted on the clinical front line. An algorithm incorporating relevant variables such as age, UV radiation exposure status, and histologic subtype will direct genetic investigations in a way similar to that of pathology-supported genetic testing in breast cancer (Fig 1).[70,71] Table III shows examples of

clinical and pathologic factors associated with specific genotypes. The incorporation of genomics could refine traditional clinicopathologic classifications of melanoma.[75]

### Treatment: targeted therapies

In 1 large study of melanoma, including acral melanoma, the majority of tumors contained a potentially actionable target with currently available therapies.[23] At present, treatment of *BRAF*-mutated melanoma with a combination of BRAF and MEK inhibitors offers rapid, albeit partial, responses in many cases.[12] This pathway is less relevant to the treatment of acral melanoma. Less is known about the role of therapies targeted against other melanoma mutations, although studies show some efficacy (eg, *KIT*-mutated melanoma treated with tyrosine kinase inhibitors).[12] Although these therapies are currently prohibitively expensive in many settings, patients may access them through clinical trials, and they are likely to become standard of care. Table IV refers to current and potential treatment strategies for melanoma. A combination of agents will better address the complexity of tumor and host biology. Agents currently under development may have a place in acral melanoma treatment.[18,22,31,44,82,89]

### Prognosis

Individualized prognostication in melanoma will incorporate genetic analysis.[90] At present, certain genetic lesions found in melanoma confer worse prognosis; for example, *NF1* mutations, *TERT* amplifications and mutations, *AURKA* copy gain, and some mutational signatures.[22,32,52,91]

### Prevention

Specific recommendations for the prevention of acral melanoma remain elusive. No major mutagenic driver is confirmed, as in UV-induced cutaneous melanoma.[3] Predispositions such as a history of penetrating injury or physical strain are proposed.[5,92] Multiple melanocytic nevi on the foot was identified as a risk factor; however, it is unusual for acral melanomas to arise in existing melanocytic nevi.[3,92]

## OTHER MOLECULAR AND MICROENVIRONMENTAL FEATURES

Although not the focus of this review, microenvironmental factors have an important role in explaining acral melanoma pathogenesis, treatment response, and prognosis. This ecosystem includes epigenetics, proteomics, metabolomics, the tumor microenvironment, and the host's immunologic response, germline mutations, and even microbiome.[4,12,15,31,67,93-102] Of particular importance are immunology and germline mutations.

A critical step in melanoma development is the ability of the tumor to evade detection by the immune system. This pathway is exploited by immune checkpoint inhibitors in the treatment of melanoma.[12] Coordination of the immune response with therapies targeting oncogenes is a possible treatment strategy.[12,89]

*CDKN2A, CDK4, MCR1, BAP1,* and *TERT* promoter germline mutations increase melanoma risk within families.[15,96,97] No specific germline mutation is associated with acral melanoma yet; in fact, *MCR1* variants were less common in acral lentiginous melanoma patients in a Swedish study.[103] An increased risk of melanoma in general (but not acral lentiginous melanoma specifically) was observed in families of acral lentiginous melanoma patients.[104] One study showed a similar prevalence of acral lentiginous melanoma in a cohort of melanoma patients with familial *CDKN2A* mutations compared with a group without.[3,105] Patients with multiple primary acral melanomas (but no family history) have been reported.[106] An uncommon association of melanoma and some forms of inherited palmoplantar keratoderma has been reported (Mal de Meleda, Papillon-Lefèvre syndrome, Nagashima-type disease, and Greither disease).[106-110] Mutations identified include *SLURP-1* (Mal de Meleda), *CTSC* (Papillon-Lefèvre syndrome), and *SERPINB7* (Nagashima-type disease). It is not clear whether these cases were a result of inherited predisposition to melanoma or another intrinsic susceptibility.

## CONCLUSION

Critical knowledge gaps in the tumor genetics of acral melanoma remain. Complete molecular characterization of acral melanoma subsets, including different anatomic and histologic subgroups, is necessary. The development of pathology-supported genetic testing algorithms will herald the age of precision medicine in the treatment of acral melanoma. Clarity about the molecular events leading to progression and metastases, and whether these are unique in acral melanoma or even in acral melanoma subsets, will be helpful to explain treatment success and failure. Understanding how intratumoral and intertumoral heterogeneity leads to the biological behavior of acral melanoma is critical. The ultimate goal is unraveling the molecular events leading to acral melanoma development in the first place and to apply this knowledge to prevention and treatment.

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