Causation and melanoma classification

Brendan Clarke

PhD Candidate
Department of Science and Technology Studies
University College London
Gower Street, London, WC1E 6BT
b.clarke@ucl.ac.uk

Abstract

In this article, I begin by giving a brief history of melanoma causation. I then discuss the current manner in which malignant melanoma is classified. In general, these systems of classification do not take account of the manner of tumour causation. Instead, they are based on phenomenological features of the tumour, such as size, spread, and morphology. I go on to suggest that misclassification of melanoma is a major problem in clinical practice. I therefore outline an alternative means of classifying these tumours based on causal factors. By analogy with similar systems that have recently emerged for other cancers, I suggest that this causal classification is likely to be both workable and helpful, even in the absence of a full causal-mechanistic understanding of the aetiology of the tumour.

Keyword: Melanoma, classification, causation, mechanism

Malignant melanoma

Malignant melanoma is a common tumour of the melanin-containing cells of the skin. The first modern description of the disease dates from the 1806 work of René Laënnec [1, 2], and the first description in English dates from an 1820 work by William Norris [3, 4]. The term `melanoma' itself was first used by Robert Carswell in the 1830s [5]. We have good evidence, though, that people were developing melanoma long before the nineteenth century. For example, pigmented skin tumours were described in the Hippocratic corpus during the fifth century BCE, and evidence of metastatic melanoma has also been found in human remains dating from a similar period [6].

By the late nineteenth century, many phenomenological features of the disease were well understood. For instance, by 1899, Humphry Rolleston was able to present a detailed description of a case of metastatic melanoma[1] affecting the liver:

> In this case the diagnosis was perfectly easy, as the history of removal of a melanotic sarcoma from the right eye left very little doubt that the enlargement and nodular condition of the liver was due to recurrence in that organ. As a proof that this diagnosis was correct the presence of melanin in the urine was all that was necessary; but another proof which would if present have further clinched the diagnosis was the presence of secondary melanotic nodules in the skin. The occurrence of secondary melanotic sarcoma in the liver is well known and is such a striking morbid lesion that once seen—and all museums have specimens illustrating it—it is never forgotten. [7, p. 1273]

The clinical features, natural history, progression, complications, and investigative findings of melanoma were so familiar to the author and, presumably, to his audience—readers of a general medical journal—that they needed no elaboration.

However, from the contemporary perspective, Rolleston's comments regarding tumour aetiology appear startling. For instance, he suggests that most melanomas arise within the eye, while cutaneous melanomas occur rather rarely. This is the reverse of current opinion. Different too is his understanding of the pathological nature of melanoma:

> From the unsettled state of opinion at the present time some authors prefer to speak of the pigmented tumours... as ‘melanomas’ or simply as ‘pigmented tumours’, without labelling them as ‘sarcoma’ or ‘carcinoma’. In the meanwhile we should judge each case on its microscopic merits and not assume that a pigmented tumour is necessarily sarcomatous. It is not, as far as can be seen at present, a matter of any great clinical importance what the exact structure of a malignant melanoma is, though more careful classification in the future might be expected to show that there was some difference in the rapidity of generalisation. [7, p. 1274]

As might be expected, this aetiological indifference was controversial. George Clarkson argued that Rolleston missed the significance of the causation of the tumour: ‘One cannot,

[1] ‘Melanotic sarcoma’ is Rolleston's terminology.

however, help being struck by the fact that though he has carefully summarised the present state of our knowledge of the subject of primary pigmented tumours, the most important links of the chain are yet wanting and very little is definitely known of their true nature' [8, p. 1392].

As this episode illustrates, the clinical syndrome of melanoma was well described during the second half of the nineteenth century. However, the details of melanoma tumour pathology remained controversial well into the twentieth [9]. Controversial too were questions about aetiology, in particular the relationship between pigmented moles and melanoma [10] and the types of tumour classification thought useful. I will address classification more fully in another section. First, though, I will outline the current position on melanoma causation.

Melanoma causation

So what do we now think causes melanoma? The broadest answer, such as might be found in the health promotion literature, is that UV radiation, primarily from sun exposure, is the main cause of melanoma. For instance, the Cancer Council Australia website states that 'Melanoma risk increases with exposure to UV radiation, particularly with episodes of sunburn' [11]. But while UV radiation is the primary cause of melanoma, other factors are known to be causally significant: 'Also at risk are people who have increased numbers of unusual moles (dysplastic naevi); depressed immune systems; a family history (in 10%, some having mutations in genes CDKN2A and CDK4); fair skin; and had a previous melanoma' [11].

So while melanoma causation appears to be multifactorial, most 'normal' people who develop it do so as a consequence of sun exposure. More detailed accounts of melanoma causation also largely support this role of sunlight. For instance, a recent review of melanoma epidemiology [12] suggests that while both environmental and constitutional factors appear causally important,[2] sunlight is the most important single environmental risk factor. However,

[2] Constitutional risk factors include fair skin, number of moles (melanocytic naevi), tendency to freckle, family history of melanoma or atypical naevi, Xeroderma pigmentosa, and increasing age. The main environmental factor is sun exposure, with no clear pattern of risk from other purported risk factors, including sunlamp use

the details of this relationship appear interestingly complex. While outdoor workers have very high total sun exposure and correspondingly high incidence of non-melanoma skin cancers, they have a much lower incidence of melanoma than indoor workers. This suggests that episodic sun exposure is more important than continual exposure. The ratio between types of sun exposure also seems to determine the type of melanoma that develops—that is, different types of melanoma appear to be caused by different forms of sun exposure. Finally, in a large study conducted on melanoma sufferers, those with high degrees of sun exposure had higher rates of survival [15].

In fact, recent research has further complicated this relationship. As has been recently noted, different types of melanoma contain different mutations [16]. When this is combined with the recent reviews of the genetic pathogenesis of the condition [17], it appears that the complex set of environmental and constitutional factors required to cause melanoma vary between types. For example, melanomas occurring in the absence of solar damage contain different mutations depending on their original anatomical location.[3] This suggests that the current unified conception of melanoma might be untenable, and indeed, researchers are beginning to turn to classifications based upon causes. I will outline these developments in causal classifications in a following section. Before that, however, I will detail the history of melanoma classification.

The history of melanoma classification

Leaving aside recent developments, melanoma is generally conceived of as a single pathological entity with a number of possible clinical manifestations. Melanoma classifications have generally been based on phenomenological features of these manifestations. Since the mid-1960s, when the clinopathological entity of melanoma really began to assume its modern form, there have been four main ways of classification, which are as follows:

(either UVA 320-400nm or UVB 290-320nm), smoking, hair dyes, fluorescent lighting, hormone replacement therapy, or stress. Sunscreen use seems to positively correlate with melanoma risk, but the research is heavily confounded and controversial (see, e.g. [13]; [14]). One author notes, 'there have been no studies in humans, to date, that clearly demonstrate that the use of sunscreens alone can reduce the risk of melanoma' [12].

[3] Cutaneous melanomas have high frequencies of BRAF/N-RAS mutations, while both acral and mucosal melanomas tend to show mutations in the CDK4 (cyclin-dependent kinase 4) or CCND1 (cyclin D1) pathways.

1. No classification. For example, Ackerman [18] denies the possibility of a useful classification of melanoma.
2. Classification by morphology of primary tumour:
    a. Morphological classification by gross appearance. Examples include Clark-II [19].[4]
    b. Morphological classification by tumour microstructure or invasion. For example, both the Breslow thickness [20] and the Clark level [19] are based on the depth to which tumour cells invade underlying structures.
    c. Morphological classification by both macro- and micro-features. See, for instance, McGovern et al. [21].
3. Classification by site of origin. For instance, ICD-10 [22].
4. Classification by a combination of features of both primary tumour and metastases. For example, the AJCC system [23], which is a combination of the Clark level, ulceration and tumour thickness of the primary tumour, and nodal or distant metastases.

Textbox 1: Examples of melanoma classifications

1. Clark et al. (1969) [19]
This paper contains two systems for melanoma classification, which I have dubbed Clark-I and Clark-II. Clark-I, also known as the Clark level, is well-known and still widely used. But originally, Clark-II was the primary system of classification while Clark-I was used as a subclassification within melanoma types.

Clark-I: Classification based on the level of deepest tumour invasion. The lower the level, the worse the prognosis.

Level I. Melanoma confined to the epidermis (melanoma in situ)
Level II. Invasion to the basal layer epidermis
Level III. Invasion to the papillary dermis
Level IV. Invasion to the reticular dermis
Level V. Invasion to the subcutaneous fat

Clark-II: This is a histogenetic classification of three specific types and one catch-all.

1. Superficial spreading melanoma
2. Lentigo maligna
3. Nodular melanoma

[4] Clark [19] confusingly presents two systems of classification. I have dubbed this first system, based on gross tumour appearance, 'Clark-II', while the other, more commonly encountered system is known as the 'Clark level', or 'Clark-I' as I have dubbed it. See appendix for details.

4. Melanoma NOS (not otherwise specified)

With the addition of a fourth histogenetic type—acral—by McGovern et al. in 1973, this classification system is still in common clinical use. At the time of its inception, it subsumed many other attempts at classification, including the Petersen pigmented flare [24, 25], and Trapl's horizontal/vertical system [26].

2. Breslow (1970) [20]

Commonly known as the Breslow depth, this system has been adapted to form part of other schemes, e.g., AJCC. The system classifies based on maximum lesion thickness.

I. < 0.76 mm
II. 0.76 - 1.50mm
III. 1.51 - 2.25mm
IV. 2.26 - 3.00mm
V. > 3.00mm

3. American Joint Committee on Cancer (AJCC) Staging System for Cutaneous Melanoma (1988, 1992, 2002) [23]

This is a combination scheme, primarily used for staging. It combines the features of the primary tumour (Clark level, Breslow depth, and presence or absence of ulceration) with features of lymph nodes and distant metastases. Tumours are classified as TxNyMz. Particular groups of TNM are then combined to give stage 0-IV. For instance, stage IIa is T2bN0M0, T2bN0M0, with a 5 year survival of 77-79%.

T1. Thickness ≤ 1.0mm
  a. no ulceration and Clark level II/III
  b. ulceration or Clark level IV/V
T2. Thickness 1.01-2.0mm
  a. no ulceration
  b. ulceration
T3. Thickness 2.01-4.0mm
  a. no ulceration
  b. ulceration
T4. Thickness > 4.0mm
  a. no ulceration
  b. ulceration

N0. No evidence of nodal metastasis
N1. 1 node
  a. micrometastasis
  b. macrometastasis
N2. 2-3 nodes
  a. micrometastasis
  b. macrometastasis
N3. 4 or more metastatic nodes, or matted nodes, or in-transit metastases/satellites and metastatic nodes

M0. No evidence of metastasis to distant tissues or organs
M1. Distant metastases
M1a. Distant skin, subcutaneous or nodal metastases

M1b. Lung metastases
M1c. All other visceral metastases or any distant metastases

4. ICD-10 (2007)

This is a simple melanoma classification based on the site of the primary lesion.

C43 Malignant melanoma of skin
C43.0 Malignant melanoma of lip
C43.1 Malignant melanoma of eyelid, including canthus
C43.2 Malignant melanoma of ear and external auricular canal
C43.3 Malignant melanoma of other and unspecified parts of face
C43.4 Malignant melanoma of scalp and neck
C43.5 Malignant melanoma of trunk
C43.6 Malignant melanoma of upper limb, including shoulder
C43.7 Malignant melanoma of lower limb, including hip
C43.8 Overlapping malignant melanoma of skin
C43.9 Malignant melanoma of skin, unspecified

So most systems of melanoma classification have used characteristics related to tumour structure, morphology, extent, or location to do their classifying. In general, they have proven rather unstable. Newly introduced classifications have tended to be popular for brief periods before rapidly being replaced by newer ones [27]. There are a couple of exceptions—in particular, the Clark level and the Breslow thickness—but the general impression is that they are transient. Later classifications tended to be more complex than the earlier ones. This seems to have been a result of the monistic tack taken by many of the authors. Useful past attempts at classification are not added to. Rather, they are replaced, or at best modified, and subsumed into an altogether novel system. Take the example of the Breslow depth [20]. A similar invasion-based classification persists in, for example, the AJCC's 2002 classification system [23]. However, the actual depths of invasion that form the category boundaries employed in the classification have changed.[5] Thus, there are important differences between the literature on melanoma classification and the manner of melanoma classification in practice. This manifests itself in, for example, the monism of published systems of classification versus the pluralistic employment of melanoma classifications in practice. For instance, in a recent article [16], trial participants were initially partitioned into 'mucosal', 'acral', 'cutaneous', and 'cutaneous with signs of sun damage' groups. I could not find any

[5] See Textbox 1 for details.

publication suggesting such a system of classification. However, it does share features with two morphological classifications, namely, that by gross appearance (e.g., Clark-II [19]) and by both macro- and micro-features (e.g., McGovern et al. [21]).

Apart from these general melanoma classifications, there are also two classification types, staging and grading, with more specialised purposes. Staging is generally used as a tool to assess disease progression in a single case or to easily select and describe trial populations. As is the case for many other malignant diseases, melanoma staging systems are generally arranged along the TNM lines. This involves giving a numerical grade for T, the tumour stage (diameter or thickness, for example), for N, the extent to which the disease involves the lymph nodes, and for M, the degree, if any, of metastasis seen. The outcome of a classification can then be recorded in a three-figure shorthand to indicate the state of the disease. So an individual with a small primary tumour without nodal or distant metastasis might be described as having a T1N0M0 disease, while someone unfortunate enough to have an advanced primary with nodal and distant metastasis would have T3N1M1. Groups of TxNyMz can then be aggregated to give a single figure staging result 0-IV (see Textbox 1). This gives clinicians a useful shorthand with which to discuss the prognosis of a particular case or researchers a way to pick trial subjects at particular disease stages. The AJCC scheme [23] is an example of such a staging system.

Staging does not say very much about the cytological nature of the tumour itself. Grading, on the other hand, does. This is a specialist histopathological tool, which involves describing the appearance of tumour cells under the microscope. Relatively normal looking tumour cells are said to be low grade, while highly abnormal looking cells are high grade. In general terms, the higher the grade, the faster the tumour will grow. Tumour grade, often in concert with other types of classification, forms an important part of prognosis predictions and therapy selections. One reason for why I have not given examples of grading systems is that the gross morphological classifications are often taken as simple indicators of likely tumour grade. For example, lentigo maligna tend to be of a lower grade than superficial spreading melanomas.

In general, melanoma classifications tend not to work very well. This applies not only to the primary purposes of classification in medicine—something that I will discuss in the next section—but also to their ability to partition tumour types without question-begging. There may be, for example, tumours that are not easy to cleanly classify using these systems. For instance, under Clark-II, dividing lentigo maligna from nodular melanoma often seems to require the classifying clinician to make a decision on tacit grounds about the appropriate category.

Melanoma outcomes also suggest that these classifications are suboptimal. For example, the incidence of melanoma is steadily increasing in many parts of the world despite the current public health efforts to curb its rise. Further, and unlike most other skin cancers, the prognosis remains fairly dismal, with an overall case fatality rate of about 20% [12]. Given this figure, though, we have great difficulty predicting which tumours are likely to do well and which are likely to lead to the death of the patient. While about 80% of small, thin, and localised melanomas can be cured surgically, this is not the case with metastatic disease, which has a 5 year survival rate of about 5-10%. I will outline just how classifications may affect these measures in the next section.

Types and purposes of classification

What is all this classification for? I suggest three main purposes. The first is classification for epidemiological data collection. As I discussed above, different forms of melanoma appear to have different aetiologies, particularly with regard to the nature of sun exposure. Thus, several classifications consider markers of sun exposure—such as primary tumour site or signs of sun damage on surrounding skin—as important classificatory features. Given such a classification based upon markers of sun exposure, the relative incidence of different tumour types can be used to estimate the effective magnitude of sunlight as an overall cause of melanoma. Thus the choice of classification system will play a vital role in shaping the way in which aetiological research is performed.

The second purpose is for prediction, especially for prognostic purposes. Metastatic tumours usually have a much worse prognosis than localised ones. Most classifications take

into consideration the extent of the tumour. This allows for data collection about survival for a particular tumour spread, and thus helps with decisions about prognosis for individual cases. Staging systems are important examples of classifications designed to deal with prognosis.

The third purpose is as a guide to therapy. Different types of tumour (not to mention different grades and stages) require different treatments. As an example, deeply invasive melanomas will require different surgical management practices than superficial ones. In this case, a surgeon needs to know what sort of melanoma she is dealing with in order to make such decisions. As, for example, clinical guidelines detailing appropriate management practices employ systems of classification to describe the various forms of the disease encountered, she will need to understand and employ a variety of classificatory systems in order to properly manage an individual with melanoma. So this third purpose of classification is in some ways parasitic on data collection and prognosis. There are also cases where classification and therapy are more directly related, as in the case of specific targeted treatments such as imatinib.[6]

As can be seen from this short outline, the various tasks that classifications serve are intimately linked. The system of classification used to do aetiological research will tend to carry over into trials of treatment. From there, it will also tend to be used to assess prognosis and outcomes of treatment. This link between activities and classification, I suggest, makes it difficult to appraise systems of classification. For instance, heterogeneity within treatment outcomes may not be apparent if, in our system of classification, we cannot describe what it is that distinguishes cases. Similarly, features of cases that could be useful in classification may be neglected. See, e.g., a 1965 article 'Malignant Melanomas of the Skin' [29] for an early description of the confusion that can result.

[6] Imatinib is a recently developed chemotherapeutic agent which has become widely used in the treatment of cancers, including chronic myelogenous leukaemia (CML). It acts via a specific inhibition of certain types of tyrosine kinase enzymes (TK), which play a vital role in cell signalling. The types of TK inhibited by imatinib include the cytokine receptor c-KIT, which appears to play an important role in melanoma aetiology. I discuss the significance of this for imatinib as a possible therapeutic agent for melanoma in the 'Causal classification of melanoma' section.

Some have argued for strongly unificatory classifications of melanoma—that is, one that gives up on intra-melanoma classification altogether. I strongly disagree with this suggestion. I think that the rewards of classification are worth all the conceptual and empirical bother. In fact, it appears to me that the (recorded) differences between types of melanoma have already suggested the possibility of a better classificatory system than those in widespread clinical use. Such a classification system would, as I propose in the next section, be based on causes.

Causal classification of melanoma

If we are to keep classifying melanoma, what is the alternative to classification systems that are based on tumour features? I suggest that a resurgence in aetiological classification is underway in the medical literature. Instead of the previous arguments about the aetiology of the tumour, though, this modern version generally uses specific genetic mutations as grounds for classification. Importantly, these identified mutations are generally thought to play a significant causal role in carcinogenesis [16].

By ‘causal role’ I mean something quite specific. Lots of phenomenological tumour features play some sort of causal role. For instance, the bulk of a large tumour may cause the death of a patient. Similarly, the degree of invasion of a tumour may cause its metastasis—for example, when tumour cells invade a blood vessel. However, when I refer to a ‘causal role’, I wish to impose two restrictions and a proviso on the sorts of causes that are admitted. First, I am interested in the direct aetiology of the tumour. Therefore, it is the question, what features caused this tumour to come about in the first instance? that I wish to address. Why? I contend that thinking about aetiology in this way provides a number of advantages for a system of classification. First, thinking about causes in this way suggests the means of intervening on the tumour—perhaps by modifying or blocking part of the pathological mechanism. Second, if this system of working is used, one is likely to be able to make judgments about tumour features that are stable across a range of background conditions. So if a researcher finds, say, a causal genetic marker that increases the speed with which the tumour invades, she is likely to be able to make prognostic judgments over a range of different clinical scenarios.

My second restriction is that these sorts of aetiological causal processes are most intelligible when interpreted in terms of an underlying causal mechanism. In particular, I am referring to mechanisms in the same sense that Machamer, Darden, and Craver do in their publications on the subject (e.g., [30, 31]; see also Raffaella Campaner's paper in this volume [32]). While this is not the venue for a detailed exposition, they suggest a way of thinking about causality in terms of mechanisms. Mechanisms are organised arrangements of entities doing causal activities to one another. This arrangement results in a productive continuity between upstream causes and downstream effects that may span many different levels of organisation. It is also a nonreductive account of causality, that is, each individual connection between entities is itself a causal link. While this means of understanding and representing the detailed structure of causal dependencies in a particular causal situation may therefore seem to be a rather redundant endeavour, it does offer significant cognitive leverage. For instance, one might try to understand the operations of a complicated causal process by breaking it down into a number of simpler causal processes. Ideally, each of these processes would be easier to understand and more amenable to, say, experimental investigation than the original complex cause.

So while one cannot (practically, legally, morally) attempt to induce melanoma in human subjects by exposing them to UV light, one can quite happily try to induce mutations in cultured human cells by UV irradiation. One can then perform experiments *in vitro* that attempt to discover the likely effects of UV induced malignant transformations, and so on. In a similar fashion, thinking about causes mechanistically may also permit researchers to develop and test preventive or therapeutic interventions in a way that would not be possible when considering causes holistically.

With these sorts of considerations in mind, I would like to restrict the classification of causal factors to those that can be understood mechanistically. That is, one should be able to give some sort of account of the manner in which these factors act to instantiate their effects. This effectively excludes potential factors that rely on highly implausible or unknown cellular mechanisms to achieve their effects. Thus, one will typically need to explain how a potential classificatory feature makes a difference with respect to tumour cells. In common with the

vast majority of the technical literature on tumour causation, this leaves me in a monistic position with regard to causality.

One important proviso exists: such classifications can only be constructed and employed using causal features that leave some clear traces—ideally ones that can be detected easily, reliably, and cheaply—in the tumour once it has arisen. Thus, given these two restrictions and one proviso, for the time being, researchers must largely focus on genetic factors as possible features for classification.

The use of such causal factors in classification seems to offer certain other advantages to medical researchers. Typically, expected improvements in outcomes are modest for new melanoma treatments. Therefore trials of new agents are set up to typically detect single-figure movements in outcome markers. However, very often, even these modest aims are not met. Take the c-KIT mutation for example. This mutation is not found in melanoma caused by intermittent sun exposure. Only about 30% of melanomas (largely mucosal, acral, and chronic-sun exposure related) express c-KIT [33]. Imatinib, an agent that blocks the c-KIT pathway, is widely available as a treatment for leukaemia. In terms of the underlying causal mechanism, this intervention appears highly plausible, and it has also been shown to work in case reports (e.g., [34], [35]). It, therefore, seems to be a promising therapeutic candidate, in this specific subset of the disease at least.

Yet a clinical trial previously ruled out imatinib as a useful therapeutic agent, citing significant reported toxicity and no effect [36]. However, this study took patients without selecting by tumour genetics, raising the question of the importance of classification.[7] Since a large majority of melanomas do not express a c-KIT mutation, it is possible that the negative results of this trial (survival or time to progression) can be explained in terms of classification—or, at least, that any definitively negative result must wait for trials looking at the population that is likely to benefit from the treatment. Put another way, it could well be that this case is an instance of Simpson's paradox, which suggests that the direction of a statistical correlation apparent in a population may be reversed in subpopulations. Consider

[7] As far as I can see, this clinical trial was otherwise methodologically sound.

the following example from the medical literature comparing various treatments for renal stones [37]. It was found that open surgery was less successful than percutaneous nephrolithotomy in the entire study population:

Intervention	Successful outcome
Open surgery	273/350 (78%)
Percutaneous nephrolithotomy	289/350 (83%)

Table 1: Overall success rates

However, when this data was partitioned by stone size, the direction of the effect was reversed:

Intervention	Group 1	Group 2	Overall
Open surgery	81/87 (93%)	192/263 (73%)	273/350 (78%)
Percutaneous nephrolithotomy	234/270 (87%)	55/80 (69%)	289/350 (83%)

Table 2: Success rates when partitioned by mean stone diameter. Group 1: stone < 2cm, Group 2: stone ≥ 2cm.

Thus, when stone size was correlated with both treatment choice and the intervention's chance of success, there was an inversion of treatment outcomes. In a similar manner, one might expect very different treatment outcomes if trials of imatinib outcomes were to be partitioned by c-KIT status. As it is, any improvement due to imatinib is likely to be overshadowed by the much larger group of c-KIT negative subjects who have effectively received a placebo. We may, in this case, be missing out on a useful treatment just because the system of classification in use fails to cut at the most appropriate joints. Fortunately, new trials of imatinib are currently in progress using just this methodology.

So, in this case, a causal classification for melanoma appears to offer a real benefit, in part, by evading the circularity that occurs in current systems of classification. No longer would the only test of a classification system be a trial relying on the very same system. Instead, epidemiologic and therapeutic research could be supported by laboratory science in a more visible manner. Note too that doing classification causally does not require a full and detailed causal mechanism for each type of melanoma. Instead, this case suggests that incomplete causal knowledge is likely to provide a useful, albeit incomplete, means of classification.

I suggest that despite the apparent complexity of the causal situation, an incomplete classification by these sorts of aetiological factors is likely to be operational. For example, in the cases of breast cancer and certain leukaemias, partial classification by aetiology has proven both workable and worthwhile. In the case of breast cancer, current UK practice guidelines [38] require that samples of invasive disease be tested for two specific aetiological factors: estrogen receptor status (ER) and human epidermal growth factor receptor 2 status (HER2). These receptor statuses guide both prognosis and treatment, employing tamoxifen and trastuzumab, respectively.[8] Similarly, cases of Philadelphia chromosome-positive chronic myelogenous leukaemia are now routinely tested for BCR-ABL expression. Again, this is significant for both prognosis and guiding therapy, although in this case the therapeutic agent is—like that for the treatment of melanoma—a tyrosine kinase inhibitor such as imatinib. Determining the presence or absence of, for example, c-KIT mutation appears no more technically challenging than tests currently and routinely used in clinical practice for these conditions.

There are further benefits that arise from employing systems of melanoma classification that take account of causation. As causal relationships are expected to be more robust and generalisable than noncausal correlations, causal classifications should lead to better treatments than classifications based upon noncausal features. This benefit would arise, in part, from the likely improvements seen in evaluating these agents.[9] If epidemiological research is conducted using a causal classification, one should expect therapeutic trials to classify in the same way in order to give more reliable results. That is to say, one should expect not to miss positive results (as potentially happened in the c-KIT case). Similar benefits in prognosis research can be expected by much the same mechanism. Finding causes is also likely to lead to benefits in epidemiology. Once some causal factors are understood, the current mess of interdependent, complex risk factors becomes rather more amenable to analysis.

[8] A range of further biomarkers are currently employed in research contexts; see, e.g., [39].
[9] There might also be a direct benefit from thinking causally, in that one can then develop specific targeted treatments more easily.

I suggest too that the strategy of looking for causes—rather than risk factors—has a number of beneficial effects in itself, even if mechanistic causes are not discovered. For example, it may well prompt investigations of risk factors, leading to possibly revealing insights into their effects. It may draw attention to conceptually problematic areas in our understanding of melanoma classifications. In other words, systems of classification will no longer fail silently. It may alert the researcher to the presence of possible confounding factors or biases. In the current situation, most classifications of primary tumours allow the operator a degree of free judgment to classify tumours into one category or another, even if they do not really belong there.[10] But because classifications based on specific, dichotomous causal factors are much less amenable to this sort of approach, vagueness and confounding within classification systems are highlighted, rather than left hidden. Researchers may be able to draw conceptual parallels between pathological mechanisms with some degree of abstraction. An excellent example of this is the role of tyrosine kinases in oncogenesis, as discussed above. Finally, it may assist researchers in their attempts to develop interventions.

In conclusion, perhaps the answer to some of these issues with classification is to adopt a more pluralistic attitude. Causal classification is compatible with other classification systems in current use. In particular, staging and grading systems can—relatively easily—be adapted to employ causal factors rather than risk factors or tumour features. One should neither seek to rewire all existing systems of classification with causal factors nor replace them all with some new causal classification, as appears to have been the case in previous attempts at adding new melanoma classifications. One should, instead, be pluralistic about causal classifications. This suggests that something like Dupré's promiscuous realism [40] might be an ideal solution. According to Dupré, multiple systems of classification may happily coexist. Speaking of the tendency of distinct groups to classify the same objects differently, he argues, ‘diverse groups of people require workable classifications that enable them to communicate among themselves and to members of other such groups, record information... and so on’ [40, p. 204].

[10] This is generally talked about as operator dependency.

While I am highly sympathetic to this approach, I do not mean to suggest that all current systems of melanoma classification are likely to be equally empirically successful. Rather, I want to suggest that employing a classification based on causation within a pluralistic framework is the best way to proceed. Even if attempts to classify causally are unsuccessful, this strategy of attempting a causal classification is an excellent way to proceed to achieve better health care outcomes. Thinking about causes does not require thinking only about causes.

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