Tracking Medical Interventions that Target Cancer Kinds

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Abstract

Recent philosophical study of cancer identifies the functional role cancer plays in evolution by selection. Approaching cancer from an evolutionary perspective is one way to understand and model cancer progression and metastasis within the life cycle of an organism, as well as cancer’s own evolutionary history, such as in transmissible cases that survive their host. However, cancer’s role in natural selection is only one part of the story. In this paper, I defend what seems to be an unpopular approach to cancer among contemporary philosophers of biology and medicine. Inspired by a case study in canine oncology, I will investigate the molecular or biomarker approach to cancer studies and discuss how its attention to cancer’s molecular diversity is important for classifying different cancer kinds and corresponding cancer treatments. One overarching aim of this paper is accessibility to other philosophers who are interested in what philosophy can offer to cancer studies from a non-evolutionary vantage point. And so, I also discuss some non-evolutionary puzzles to be reckoned with in addition to contrasting two methodological approaches to cancer: evolutionary modelling and molecular biomarker identification. I argue that there is still much to be learned through a philosophical study of cancer within a non-evolutionary framework; its promise concerns how clinical classification programmes are instrumental to scientific success.
1. Introduction and Motivating Factors

There is recent attention in philosophy of cancer to the role cancer plays in evolution by selection (Germain 2012, Lean and Plutynski 2016, Germain and Laplane 2017). Approaching cancer from an evolutionary perspective is one way to model populations of cells as evolving through time. While this is important work, there is much to be learned through a philosophical study of cancer from a clinical, rather than evolutionary, perspective. Clinical experiences are primarily local and individualized lived experiences, which calls for a mindfulness concerning how philosophical work tracks medical intervention in clinical settings. In this paper, I defend an unpopular approach to cancer investigation. I aim to conduct an accessible, non-evolutionary investigation concerning how classificatory practices are instrumental to therapeutic success and medical knowledge generated in this context. The defense includes some criticism of recent attention to evolutionary modelling of cancer in philosophy of biology.

Evolutionary approaches aim to understand cancer’s broad functional activity in natural selection. This includes whether cancer cells exhibit complex adaptations as properly construed objects in selection, such as whether changes are cumulative across populations of cells, or if changes are “one shot” like mutations that encompass the loss of some regulatory mechanism rather than the production of something new (Huang 2011). What’s potentially at stake in the evolutionary debate is how cancer co-opts bodily functions to advance its own fitness. In fact, cancer progression might have its own evolutionary history: The best cases supporting cancer as the emergence of something new, rather than a mere by-product of selection, are transmissible pathogenic cases. For example, facial tumors in Tasmanian devils, venereal cancers in dogs, and the infamous HeLa cells, all include cancerous cells that survive and thrive
beyond the death of their host marking an independent evolutionary path. Often an evolutionary approach to cancer progression is motivated by its potential for therapeutic success:

“Indeed, taking an evolutionary perspective may assist in cancer treatment, such as demonstrating when and why it is better to use combinations of drugs to treat cancer” (Lean and Plutynski 2016, 41).

“[T]he promises of an evolutionary perspective on cancer—which purports to explain the very urgent problem of tumor relapse—are attractive. The new approach, if heeded, would imply a major reorientation of research programmes in molecular oncology, and a reshaping of clinical practice” (Germain 2012, 786).

“Evolutionary and ecological approaches to cancer research emerged in response to the lack of clinical applications from the basic biology discoveries...a primary goal of evolutionary medicine is to have clinical impact” (Liu 2018, 228, 232).

“The evolutionary dynamics that yield this [i.e. becoming better adapted to a host’s immune defenses] progressive adaptation are germane for fine tuning treatment regimens to increase their effectiveness...both cancer and infectious diseases have underlying clonal evolutionary dynamics that are specific to that individual and depend on a variety of local circumstances” (Liu, Love, & Travisano 2017, 107, 109).

Throughout much of this work there is an undercurrent that traditional biomarker approaches, i.e. molecular attempts to identify a mechanism of cancer on which to intervene with targeted therapies, have in some sense failed to get us where we need to be clinic-wise, that its progress is not fast enough, and that it is insufficient to capture complex cancer progression in the cancer types that have vastly heterogenous profiles. And so, here I will defend what now appears to be the rather unpopular biomarker approach among philosophers
of biology and medicine against the charge that it is failing to do the work we need. Despite this, I’ll end with a pluralist line that while evolutionary modelling is important and should continue, it’s translational relationship to medical practice needs clarification.

In what follows, I first motivate and explain Somatic Mutation Theory—a guiding catalogue that identifies markers or mechanisms important for cancer classification. Then I briefly survey some puzzles concerning cause and effect, reductionism, intrinsic properties, and identity to demonstrate the need for philosophical insight in a non-evolutionary context. Because clinical therapies rely on molecular classifications, I show why mutations matter for classifying cancer kinds. From a non-evolutionary vantage point I emphasize the importance of mutations and mutational patterns in classifying different cancer kinds. I also show how medical intervention draws from those classifications in a case study inspired by canine oncology. Investigating the influence of stochastic processes—processes not biased to the environment like mutations—moves away from functional adaptation talk and selection, and towards an account of cancer that emphasizes intrinsic structural characteristics of oncogenic cells.¹ While investigating mutational profiles and biomarkers of cancer is not new, it turns out that cancer classification practices reveal interesting philosophical questions to be explored.

2. From a Non-Evolutionary Framework: Different Cancer Kinds, Somatic Mutation Theory, and Why Mutations Matter

In this section, I’ll motivate a focus on intrinsic cellular features (i.e. biomarkers or mechanisms), such as their role in cancerous activity and how mutations shape cancer

¹ Generally, McConwell (2017) encourages shifting focus to the role of chance both in the history of life and within the developmental lifecycles of organisms.
classification practices. There are, of course, philosophical nuggets of interest concerning cancer and mutation, such as questions about cause and effect, reductionism, and identity, which I briefly survey. Such puzzles arise when considering a molecular approach to cancer research, such as Somatic Mutation Theory (SMT); a running catalogue of genetic changes (Baker and Kramer 2007). Keep in mind that both this current section and the next—a molecular mutational focus and thereafter a case study from canine oncology—set up for lessons concerning how cancer classification schemes guide epistemic inquiry and lead to success as means for intervention and positive clinical outcomes.

2.1 Somatic Mutation Theory: Theoretical and Empirical Grounds for a Molecular Focus

Before turning to puzzles concerning cancer, here I introduce two selected themes to both explain and motivate the molecular approach.

First, approaching cancer at the molecular level includes grappling with randomness, but it’s not a disorganized mess beyond comprehension. Focusing on somatic (or non-reproductive) cell mutations concerning cancer dates back to the early 1900s (Tokheim 2016, 3). The last forty years has produced a strong effort to identify mutations associated with tumors comprising a catalogue of those mutations or ‘oncogenes’ (ibid). There are many different types and causes of mutations, but generally mutations are considered random changes in the nucleotide sequence of an organism’s DNA.\(^2\) Using the term ‘random’ is contentious: Noble (2013, 1236) states that the question is not whether changes are truly random, instead one should ask

\(^2\) Examples of different types of mutations are (1) deletions where a piece of DNA is removed, (2) duplication, which includes DNA that is copied one or more times, (3) insertion, which changes the number of DNA base pairs in a gene, and (4) substitution where one base (i.e. a “chemical letter” like A or G) is switched to a different base.
whether they are “chance events from the viewpoint of function.” Arguably, mutations are characterized as random due to the post-Modern Synthesis sentiment that privileges the role of environmental fit and function through natural selection, rather than internal developmental constraints and history (see Gould 2002). ‘Random’ here does not mean that the occurrence of prior mutations is irrelevant. For example, Kent and Green (2017) argue that the order of individual mutations acquired determines the cellular and molecular properties of tumor initiating cells. This means that often mutational history matters to cancer classification: randomness does not necessarily imply a haphazard lack of constraint. At the very least, mutations can be used to organize different cancer types as we’ll see.

The cataloguing of cancer genes guided by Somatic Mutation Theory (SMT) is based in genome sequencing. Historically, SMT represented cancer as a cell-based disease concerning interior workings of cells—e.g. problems with out of control proliferation and abnormal chromosomal rearrangement— as the causes of cancer (Soto and Sonnenschein 2014). Generally, the aim is to impose some order on nucleotides that make up cancer DNA through molecular techniques, which has been immensely successful for classification practices based on evident mutations. I discuss this in more detail with a case study later on.

Randomness or stochasticity informs how genetic instability is conceived in molecular frameworks. Cancers considered as deviations from the original organism DNA sequence draw from research on genetic instability. There is often a mechanistic understanding of genomic alteration mechanisms, such as chromosomal crisis or shattering (chromothripsis) and mutation

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3 SMT has been criticized for switching the default state of cells from proliferation to quiescence (i.e. a state of inactivity), which introduces the need for initial stimulators in the form of oncogenes (or genes in the cancer genome) with “no biological reality” (Soto and Sonnenschein 2014).
storms (kataegis); accounts which detail how the process unfolds rather than denoting any particular cause (Wang 2013). For example, chromosomal shattering includes significant numbers of rearrangements in specific regions of the chromosomes, while a mutational storm occurs when there is a pattern of mutations clustered in small genomic regions (Forment et al. 2012). These mechanistically-described changes are only a few of the ways genetic instability is expressed, but generally “genetic mutations arise as part of a stochastic cascade of mutations on the way from an initial mutated cell to malignant cancer” (Baker and Kramer 2007).

Stochastic DNA replication “errors” can lead to mutations—every time a cell divides its DNA replicates, and that DNA is copied and transmitted to its daughter cells. Sometimes mistakes occur in that process, which pushes for a medical focus on intrinsic factors: “Random mutations arise in normal stem cells during DNA replication, and the mutation rate is proportional to the cell proliferation rate” (Alekseenko et al. 2016. 800). In other words, the higher the mutation rate, the unrulier cellular production can become. And because the out-of-control proliferation of cells is one hallmark of cancer, understanding how and which mutations initiate that process is imperative for screening and subsequent treatment. This point is covered in the case study from canine oncology in section 3.

The concept of genetic instability is worth another look, however, because chance often takes a secondary role in evolutionary accounts of cancer progression. The forms of genetic instability identified above (i.e. shattering and storms) have a significantly stochastic or random form, which exhibit variation in ranges of patterns even under the same conditions. But, there

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4 The role of chance is downplayed in evolutionary accounts in favour of selectionist processes, for example, in debates over whether cancer cells exhibit complex adaptations or mere (large or small) mutational effects that are “irrelevant to whether [a trait] is in fact an adaptation” (Lean and Plutynski 2016).
is a form of repetitive instability with fragility evident at a particular sites under certain conditions, such as chromosomal instability in old cells where aging genomes experience random DNA breakage and decreased cohesion capacity as cells age (Sangita et al. 2018). Sangita et al. argue that the global loss of cohesion in old cells is the cause of increased rDNA instability. To be clear, it seems as though there are at least two different senses of instability:

1. Genetic instability that is significantly stochastic or random in form, e.g. the mechanistically-described cascades of chromosomal shattering and mutational storms

2. A repetitive instability with fragility at certain sites and under certain conditions, e.g. aging genomes that experience DNA breakage and decreased cohesion capacity as cells age

The instability in #2 is dependent and repeatable compared to the stochastic range of variation in chromosomal shattering and mutational storms in #1. What can we say about this? Certainly, increasingly stochastic forms of instability make it more difficult to identify molecular difference-makers, which initiate the mutational effects. That is, the range of stochastic variation confounds our ability to identify stable cause and effect relationships. Alternatively, in a repetitively unstable scenario where rDNA instability more reliably recurs, it may be easier to identify specific points where the same deviation or breakage happens. One might infer, then, that there are different kinds of genetic instability: some of which are more difficult to control and predict, and perhaps more quickly detrimental to the organism because of their erratic natures, and others that are repeatable and constrained by historical conditions.⁵

⁵ Thanks to Jennifer Cobb and her lab group at the University of Calgary for discussion concerning instability and cause and effect. One research theme explored in their work includes incidents of Werner’s Syndrome, which are characterized by the premature appearance of aging in young adults with an elevated risk of rare sarcomas. They
Overall, the different roles for chance here are striking both concerning the phenomena of unstable events and our capacity to represent them. On the hand, sometimes there is contingency such that an unstable even is dependent on certain initial conditions or prior pathways, such as aging and decreased cohesion. Whereas other unstable events occur in cascades that are less constrained and more haphazard. The latter case will likely be immensely representationally difficult, on the investigator’s part, to establish (and control) any cause and effect relationship, such as the shattering and storm effects mentioned above. Regardless, molecular approaches to cancer generally investigate the causes of genomic instabilities and their effects by grappling not only with randomness, and also with these different chance-driven contexts.

A second theme in addition to conceptual issues concerning randomness and genetic instability is a practical reason to care about SMT: Alekseenko et al. (2016, 800) argue that only one third of the variation of cancer risk can be explained by external factors or inheritance.\(^6\)

\[\text{Figure 1. Alekseenko et al. (2016, 800) argue that only 1/3 of cancer risk can be explained by external environmental factors (e.g. “cancer causers” like smoking, sun, and radiation) or inheritance (e.g. susceptibility}\]

\(^6\) Notably, Hollstein et al. (2017, 165) argue that mutational signatures reveal little about their author, and mutational signature analysis incriminates \textit{environmental} factors as responsible for shaping which signatures on a given spectrum are associated with a particular tumor. This is contra to Alekseenko et al. (2016) who emphasize endogenous (i.e. internal cause or originating within the organism) biological factors. However, both parties agree that more investigation is needed concerning signatures linked to endogenous mutational processes (vs. carcinogens or environmental cancer causers), and that the heterogeneity of signatures in a given cancer type implies a once-size-fits-all approach to early detection and therapies is misguided.
mutations passed to offspring through germline cells). This means that 2/3 of cases occur within the life cycle of organisms from causes unbiased to the environment, such as mutations. The prevalence of unbiased causes calls for a better understanding of how cancer starts.

On the one hand, external factors include specific carcinogens or “cancer causers” that alter intrinsic features of cells in response to environmental stimulants, such as smoking, sun, or radiation exposure, etc. On the other hand, inheritance includes, for example, cancer susceptibility genes, such as the BRCA1 and BRCA2 mutations that put women at a high risk of breast cancer (Baker 2017, 4). These heritable genetic mutations exist in germline cells and are passed to offspring. If only one third of cancer cases are caused by external and/or heritable factors, this means that two thirds of cases are often unpredictable in nature concerning why they start, or at least unpredictable from the view point of a selection-focused evolutionary theory concerned with environmental adaptability and heritability. In other words, a majority of cancer cases are due to random cellular mutations occurring within the life cycle of an organism and from unbiased causes (i.e. causes not biased to environmental challenges).

However, the process of natural selection includes changes within populations caused by a process bias to the environment:

![Figure 2. The orange circle indicates that a majority of cancer cases are due to mutations occurring within the life cycle of the individual organism from causes neither biased to the current external environment nor through](image-url)
heritable means. This calls for a better understanding of how cancers start in addition to the dynamics of progression.

But what is so special about unbiased causes occurring within a developmental life cycle? How most cancers start is not well understood, and if satisfying the aim for early detection and prevention is a key to battling the disease, then a better grasp of cancer initiation is needed. This doesn’t mean that evolutionary modelling of cancer progression should be stopped—it’s unsurprising that a plurality of approaches (evolutionary and otherwise) is needed. Rather, the point is that understanding the dynamics of how cancer unfolds may not explain how cancer starts. This is analogous to large-scale thinking about the origin of life versus evolutionary change:

“Most strikingly, questions surrounding the origin of life (largely an issue of chemistry and the physics of self-organizing systems) are so different from problems in subsequent evolution (issues of natural selection and mechanisms of change. The two subjects grade into each other temporally (for origin does lead to evolution!), and the public certainly views them as united...but origin and evolution pose different problems; are studied with different methods, disciplines, and even languages; and, in some deep sense, simply don’t belong together.” (Gould, B460/f8, 4).

Gould made that statement despite finding some unity in common focus among those who worked in life’s origin and evolution. I suspect that something similar is going on in cancer. If understanding cancer initiation is important for early detection and targeted treatment, and it’s unclear how evolutionary models might explain cancer initiation across organisms, then the connection between modelling cancer progression evolutionarily and targeted treatment is unclear. That is, admittedly, a mere limitation concerning the scope of modelling cancer progression’s evolutionary dynamics. However, if targeted treatment relies on identifying
mechanisms related to the origin of a particular cancer in a particular organism, one negative consequence is that evolutionary modelling needs to stay in its own lane, so to speak. At least currently, it’s not clear how an evolutionary analysis aids in targeted cancer treatment. Or at least this a challenge that needs to be clearly articulated by those applying evolutionary ideas to explain how cancer progresses. However, if there’s one thing a mutation-centric approach has going for it, it’s targeted clinical success. As we’ll see, there are also more philosophical puzzles too.

Turning towards an analysis of mutations in cancer cells, namely the changes that occur in DNA all together referred to as the ‘cancer genome,’ lends itself to increased understanding of cancer initiation. This non-selectionist picture of cancer shows how cancer’s history is rife with stochasticity at least in part due to developmental factors occurring within the life cycle of an organism. There are conundrums concerning the intrinsic structural characteristics of cancer cells, which is anything but short of philosophical fuzziness worthy of attention.

2.2 A Brief Survey of Puzzles Concerning Somatic Mutation Theory

Here I survey four puzzles as opportunities for non-evolutionary philosophical work on cancer biology before discussing why mutations matter for cancer kinds. While the survey is brief, it serves dual-purpose: not only are there salient philosophical problems arising from a non-evolutionary context, the puzzles also clarify important concepts and terminology for what follows. While the list is not definitive, it’s meant to show the potential of non-evolutionary analyses for philosophers of biology. I present the puzzles through an exchange between two approaches to cancer: Somatic Mutation Theory, which we are already familiar with here, and Tissue Organization Field Theory; a view that challenges SMT’s cellular focus.
Puzzle 1: Cause and Effect. One objection to the cellular focus of SMT serves as the first puzzle calling for the expertise of philosophers. The objection draws from disagreement over genetic instability as a consequence rather than a cause of cancer (see Baker and Kramer 2007, Bertolaso 2016). Proponents of Tissue Organizational Field Theory (TOFT) argue that cancer is caused by a breakdown in cellular communications and interactions among tissues (Baker 2017, Baker and Kramer 2007). According to TOFT, genetic instability is a consequence or result of that communication breakdown, rather than the cause(s) of cancer itself. TOFT presses the idea that cancer is a tissue-based disease: it pushes away from only analyzing intrinsic cellular changes and towards including interactions among tissues and cells, signalling, etc. (Soto and Sonnenschein 2011, Tokheim et al. 2016, 4). TOFT focuses on extrinsic or relational features that embody the complex relationships between tissue compartments. TOFT as a competitor to SMT raises the apparent dichotomy of cell-based versus tissue-based analyses of cancer (Soto and Sonnenschein 2011, also see Bertalaso and Sterpetti, forthcoming). Ultimately, the views differ in how cancer is caused:

Figure 3. According to SMT genetic instability causes cancerous cellular activity, whereas according to TOFT genetic instability is an effect of cellular communication and interaction breakdown among tissues.

So, is cancer caused by inner workings of cells or by tissue environments? There is of course a reductionist response one might give on behalf of TOFT.
**Puzzle 2: Reductionism.** Philosophers of science will be familiar with a potential line of argument given in defense of TOFT: interactions among different components of tissue cannot be reduced to cellular events (ibid). In other words, there are system-level properties irreducible to the structural features of cells. Taking TOFT as a potential objection to SMT, here is one response. In the case of cell-based versus tissue-based analyses of cancer we are not stuck in an either-or situation. We can be good pluralists about multiple scientific approaches to a given phenomenon (such as Longino 2013, 16). It is perfectly reasonable to analyze cancer through various means including any system-level properties there might be. SMT and TOFT are not necessarily in tension if we consider them different avenues of analysis to understanding the disease. Reductionism might be a theoretical concern but accepting TOFT does not entail a large-scale rejection of SMT. Additionally, one might wonder about the relationship between an evolutionary approach to cancer progression and TOFT’s analysis of interactions in the cellular environment. However, whether or not cancer cells exhibit complex adaptations may not directly inform the viability of a systems-level analysis of cancer, especially when it concerns the developmental signalling systems among cells within organisms and their internal or intrinsic structural components. Regardless, whether cancer is a tissue-based or cell-based disease is at least partly informed by what we think cancer is, which brings us to the third puzzle.

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7 Hollstein et al. (2017, 165) recommend that to understand a mutational signature, we need to know the nature of the cancer risk factor from epidemiological and patient exposure data, as well as “mutagenic and chemical properties of carcinogens and endogenous mutational processes,” which requires multiple lines of information—internal and external—to establish a cause. That mutations distinguish different cancers is one thing, but reading mutational signatures is a complex process calling for numerous lines of scientific inquiry.
**Puzzle 3: Identity.** Genetic instability as a marker of cancer stirs up questions about identity. SMT identifies cancer as genetically unstable, however, genetic instability is also evident in benign (or non-cancerous) growths and hyperplastic polyps, which are clusters of cells that can increase in number (Baker and Kramer 2007). And so, genetic instability is not associated with cancer alone. There is an identity problem here concerning how mutational processes distinguish cancer from non-cancer along with some scientific work that tracks that topic. It might be tempting to think that a particular number of mutations sets the benchmark or threshold for a cancerous cell. In fact, in 1999 it was not clear how many mutations were required to turn a normal cell into a cancerous one (Boland and Ricciardello, year). So, though the presence of mutational processes may not be the distinguishing factor, the number of mutations might be. However, recent work by Tomasetti and Vogelstein (2017) tracks the number of stem cell divisions and the risk of different cancer types, which result from certain types of “R” mutations that occur during the replication of cells. They conclude that a strong correlation exists between these divisions and cancer occurrence regardless of environment. Before turning to how types of mutations and mutational patterns are used to classify cancer kinds, there is a fourth and final puzzle that also serves to sort through some terminology.

**Puzzle 4: Intrinsic vs. Extrinsic Properties.** Whereas SMT focuses on the internal characteristics of cells, such as mutational sources of instability, TOFT defines cancer relationally in terms of its interactional properties. So, clarification concerning intrinsic versus extrinsic properties in this context is required. In the current context, by ‘structure’ I mean the
organization, arrangements, or biomechanics within cell walls from organelles to DNA.  

‘Intrinsic structural characteristics’ typically has non-accidental or essentialism connotations, so calling an accidental mutation ‘intrinsic’ might seem odd. However, Brian Ellis distinguishes between properties that objects have independently of outside forces acting on them (intrinsic) and properties in virtue of outside forces (extrinsic). Taking seriously Alekseenko et al.’s (2016) claim that a majority of cancer risk includes mutational causes not caused by external (environmental) factors, then, demonstrates the usefulness of Ellis’s account in that context. The intrinsic-extrinsic distinction is heavily debated, however, Weatherson and Marshall (2017) point out that at minimum conflating ‘intrinsic’ with ‘essential’ is a misuse of terms. By ‘intrinsic’ I just mean the internal features of cells in the sense of structural re-arrangements that yield oncogenes. Those features are important because they are used to classify cancer types. And as we shall see, those classifications explain the success of medical interventions. This is a significant line in defense of SMT’s success.

2.3 Why Mutations Matter for Different Cancer Kinds

The intrinsic mutational architecture of cells does a lot of classificatory work. They matter for different cancer kinds. Take the following example. Alexandrov et al. (2013, 415) show how classes of tumors are distinguished by mutational processes. Some mutations cross-classify cancers and so are present in many cancer types, however, others are “confined to a single cancer class” (ibid). Alexandrov et al. say,

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8 McConwell (2019) discusses how structural diversity spans scales from organization internal to cells, among cells, to the body plans that define different phyla, and even the profile of ancestor-descendent relationships and community interactions within ecosystems. Chance-based sources of contingency, like mutation, play a role in altering these structures and cause salient differences that do not rely on differences in function. I take cancer to be a special case of the ideas proposed in McConwell’s paper.
Different mutational processes often generate different combinations of mutation types termed ‘signatures’...to generate a mutational signature, a single mutation from each cancer sample is entered into a mutation set aggregated from several cases of a particular cancer type...if multiple mutational processes are operative, a jumbled composite signature is generated (2013, 415).

A mutational signature is a pattern evident on the cancer genome defined by the type of DNA damage and repair processes that result in structural deviations (Alexandrov et al. 2014). They point out that different kinds of mutations (e.g. insertions, deletions, etc.) and any “accessory mutation characteristic,” such as their historical sequences can be included in how mutational signatures are defined. There is, then, a diversity of mutational processes underlying the development of cancers that generate these signatures. In 2013, Alexandrov et al. extracted more than twenty distinct mutational signatures, some present in many of the cancer types they studied and others confined to a single cancer class. For instance, “in most cancer classes at least two mutational signatures were observed, with a maximum of six [signatures] in cancers of the liver, uterus, and stomach” (Alexandrov et al. 2013). This indicates a “complex repertoire of mutational processes” in those cancer kinds (ibid). They focused on two signatures—1A and 1B—that were similar, but mutually exclusive across cancer types finding either 1A or 1B, but not usually both. For example, the diagram below (a simple adapted version of the figure in their paper) shows how 1B (among other signatures) is present in breast

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9 Alexandrov et al.’s work does include mutations due to environmental factors, however they note that many were of “cryptic origin,” that is, not caused by external or heritable means.

10 Alexandrov et al. do entertain speculate that the same underlying process are responsible for both 1A and 1B because of their similarity in overall pattern and correlations with age, such that with the proper data 1B would “disappear.” Regardless, the graph includes a list of 21 other signatures mapped through 30 cancer types.
and cervix cancer, but not 1A. However, prostate and stomach cancer exhibits signature 1A (among other signatures), but not 1B:

<table>
<thead>
<tr>
<th>Signatures</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>1A</td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>True</td>
</tr>
</tbody>
</table>

*Figure 4. Adapted from a larger graph in Alexandrov et al. (2013, 21) where they map 21 signatures to 30 different cancers. Signature 1A is present in 7 cancers, while 1B is present in 19. The prevalence of signatures does vary in the samples, for example, the prevalence of 1A in cancer samples was 11.7%, and 1B was 60.7%. They discuss how the prevalence of a given signature indicates where the signature contributed a significant number of mutations.*

Having a means to classifying different cancer kinds through mutational processes is valuable for its epistemic import in understanding the differences among cancer kinds. However, using patterns of mutations also has a practical upshot because the identification of mutational signatures can result in targeted, successful therapy early on, such as in the case study from canine oncology I turn to next. As we'll see, the connection between cancer classification from a molecular basis and successful therapy is obvious. After the case study I'll draw some philosophical lessons.

### 3. Veterinary Oncology and Tracking Medical Interventions

In this section I recount seeing “Dazy”—a Labrador mix—through cancer treatment as a case study. The decision-making process in clinical practice is informed by cancer research concerning the mutations or “oncogenes” that distinguish cancer kinds. Clinical practice
includes, but is not limited to, the work of oncologists administering diagnoses, prognoses, and treatment plans in hospitals and medical centers.

While in human cases, the mutational signatures in melanoma (or skin cancer) tumors determine whether a patient will respond to that therapy (Snyder et al. 2014), something similar happens for mast cell disease in dogs. Dazy was diagnosed with mast cell disease in early 2015 after finding a volatile lump near her left shoulder. At the time, this lump was no larger than the end of a pencil eraser in diameter, but was very active in terms of growing, shrinking, and opening over the course of three weeks. This turned out to be a high-grade mast cell tumor, which indicates poor differentiation between the tumor and bordering tissues and a high likelihood of growth and spread. Mast cell disease is a common, but at times very aggressive, form of canine skin cancer. Mast cells are a type of white blood cell important for the development of immunity and their malfunction (or unnecessary activation) is associated with inflammation in autoimmune disorders and allergies (Theoharis et al 2012). Mast cell tumors can release histamines resulting in itchiness and hives, particularly when the disease becomes systemic through other parts of the body (i.e. lymph nodes, liver, spleen, bone marrow). The itchiness and hives may also occur in a local manifestation if the tumor is disturbed. As I’ll discuss, patterns of molecular instability not only guide classificatory practices in cancer biology as we saw in the previous section, but Dazy’s case study demonstrates how they also support targeted clinical therapies.

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11 Tumor grading is distinct from cancer stages: grading is determined by a pathologist (or a doctor who identifies diseases by analyzing cells and tissues under a microscope), and is about the characteristics of the tumor itself, such as the amount of abnormality. This indicates the likelihood of the tumor growth and spread. Staging cancer tracks the progression of cancer through initiation to metastasis.
For canine mast cell disease, it is important to determine whether a cKIT mutation is present in the cells because these mutations are associated with unrestricted activity of tyrosine kinases—receptors with a role in cell growth and differentiation, and programmed cell death (Paul and Mukhopadhyay 2004). If cKIT expression is found to deviate from its normal state, then therapy is tailored in the form of tyrosine kinases inhibitors. The cKIT deviations are classified into patterns that indicate risk of tumor recurrence and cancer spread due to unregulated tyrosine kinase. It is here one starts moving into the depths of precision medicine.

*Figure 5: Dazy’s cancerous mast cells exhibited a c-Kit mutation with Pattern II. Diagram from the ‘Prognostic Evaluation of Canine Cutaneous Mast Cell Tumors’ from the Diagnostic Center for Population and Animal Health, [https://animalhealth.msu.edu/News/2012_Summer.pdf](https://animalhealth.msu.edu/News/2012_Summer.pdf).*
Notice in figure 2 that under the ‘histologic grading’ column a cKIT mutation might not be identified, but yet the KIT pattern—the expression of the tyrosine kinase receptor—can still deviate from the norm such that inhibitor therapy is required. Let’s zoom in:

![Decision-making process diagram]

*Figure 6. Zooming into the decision-making process for therapy guided through a molecular approach. Decisions concerning therapy are constrained by the presence of certain mutations.*

The above figure is a snapshot of the decision-making process based on what is discovered in the histology (or microscopic structure of tissues) report concerning the presence or absence of irregular cKIT patterns. The pattern indicates that the cKIT gene is stuck in the “on” position facilitating unregulated cell growth and division. Interestingly, the presence of a KIT pattern recommends inhibitor therapy even if the cKIT mutation itself has not been identified.

Since Dazy was positive for the cKIT mutation with a KIT pattern II, she underwent inhibitor therapy and is still cancer-free today despite KIT pattern II indicating a lower disease-free survival time and a mortality rate of twenty percent within ten months. However, the projected success rate for non-targeted chemotherapy was much lower. The presence of these signatures informs the decision-making process of oncologists in clinical settings so long as treatment that tracks those signatures are available. When there is no signature-specific
treatment, that is, treatment that does not target the oncogene associated with it, it’s like using a sledgehammer to pick a lock rather than a key.\textsuperscript{12}

One cited motivation for investigating cancer progression from an evolutionary perspective is its potential to assist in cancer treatment as cited in the introduction (Lean and Plutynski 2016, 41). Simply put, the idea is that if we understand progression better, then perhaps we can intervene. But how cancer functions in evolution by natural selection groups cancer as a singular functional class glossing over differences among cancer kinds. Dazy’s case shows how structural differences grounded in molecular processes are at least currently indispensable for connecting cancer classificatory programs and successful therapy. The presence of mutational signatures that classify cancers indicate whether a patient will respond to a particular therapy, in addition to serving as potential biomarkers for early detection. Next, I turn to some philosophical lessons from this case study where I further discuss the importance of embracing cancer diversity over functional sameness.


In this section I cover three philosophical lessons from the molecular approach drawn from the medical decisions made in Dazy’s case. To sum up thus far, in this paper I first defended a molecular approach to cancer by discussing the benefits of Somatic Mutation Theory, surveying some philosophical puzzles concerning cause and effect, reductionism, intrinsic properties, and identity, and showing why mutations matter for classifying cancer kinds. Patterns of molecular

\textsuperscript{12} Ash Alizadeh gives the sledgehammer vs. key description in his talk “Circulating tumor DNA analysis for personalized cancer detection and monitoring” at the Revolutions in Diagnostics Symposium at Stanford (2018).
instability not only guide classificatory practice, but Dazy’s case study shows their potential for translating to targeted clinical therapies. In other words, molecular approaches to classifying cancer kinds explains clinical success. And there are some important philosophical lessons to be gleaned from all of this for both evolutionary and non-evolutionary approaches.

Lesson 1. First, epistemic and non-epistemic values play an integral role in guiding successful intervention practices. Let me explain. Molecular inquiry concerning cancer (though of course not limited to that particular disease or area of medicine) is guided by epistemic values of precision and accuracy. Whether those values are realized is measured by what counts as therapy success, and importantly that success need not amount to a full-blown cure covering all cancer types. Rather, success might be defined on a spectrum from ideal cases where patients enter remission (i.e. a cancer-free status) to increased longevity and quality of life living with cancer. While it’s unfortunate that remission does not guarantee a life-long cancer-free status, depending on the type of cancer, which is often identified by whether certain mutations are present, the likelihood of recurrence can change. For example, while Dazy’s prognosis was dismal based on presenting mutational patterns, she’s still thriving years later.

Moreover, precision and accuracy are intertwined epistemic values: precision medicine leads to more fine-grained diagnoses, prognoses, and interventions that accurately track and predict what we know about how certain cancers start and progress. In turn, what we know about cancers is enriched by precise refinement in measurement and detection tools. Not only are targeted therapies important, but detection interventions, which yield highly specific results sensitive to particular molecular profiles of cancer types, are needed. In other words, better
traction concerning precise detection technologies will likely increase in proportion to the more we know about how cancers present molecularly. One might be concerned that molecular approaches treat cancer like an on/off switch, which excludes cancer types with heterogenous profiles during progression, i.e. many different mutational patterns among cells. Perhaps evolutionary dynamics can provide some insight when there are too many molecular targets: maybe if we can’t target the insides of the cells (i.e. because there are too many targets to contend with in some cases), we can intervene on interactions among cells. However, detection technologies and clinical practices often rely on molecular practices: higher specificity in detection might identify a local target by increasing the contrast between cancer signal and background noise, for example. Increasing detection sensitivity means catching cancer earlier when it is much smaller and tougher to find. Precision and accuracy are values that guide epistemic inquiry and are, at least in part, standards that depend on the relationship between molecular classification (i.e. in terms of mutational patterns, signals, and phenotypic presentation and activity therein) and therapeutic success. However, such epistemic values are mitigated by non-epistemic values concerning patient care. Consider the following.

There has been much work on the role of epistemic and non-epistemic values in science and medicine, but canine oncology provides a peculiar case because choices are made by the handler on behalf of the patient—a member of a different species, with whom the handler has limited access to the animal’s interior life while trying to determine what is best for the patient. However, non-epistemic values concerning socio-economic barriers, as well as patient pain and well-being mirror human cases. One the one hand, access to medical care is affected by socio-economic barriers. For example, even though Dazy was a good candidate for inhibitor therapy,
which targets cancer cells and causes less damage to non-cancer cells, that therapy was significantly more expensive and labour intensive (e.g. pills every other day) than general systemic chemotherapy administered intravenously each month. So, socio-economic barriers such as cost can overturn choices directed at achieving greater accuracy and precision in treatment. Dazy also happened to reside in a city where veterinarians specialized in oncology—a team of specialists beyond her general practitioner with an array of medical technologies was available, which is not always the case. On the other hand, reducing pain and increasing wellbeing are common non-epistemic or moral values one will consider in human and non-human animal cases alike. Detection and diagnostic measures for cancer can be incredibly invasive and unfortunately required frequently. Not only did Dazy frequently undergo biopsies of lumps of varying depth of the skin in addition to the surgical resection of the visible cancerous tumor, she also endured a biopsy of a mass on her spleen—an extremely painful experience involving a very long needle. Recall that mast cell disease can spread to other areas of the body, such as the lungs, spleen, and bone marrow. In this case, accuracy and precision trumped her wellbeing for that moment, wellbeing which was threatened by the very long needle in favour of potentially furthering life longevity. However, prioritizing epistemic values in this way does not always occur, e.g. due to the invasive nature of testing bone marrow for cancer cells, she was opted out of that procedure. There is professional recognition that less invasive detection and diagnostic measures are needed, which speaks to balancing the
relationship between epistemic and non-epistemic values.\textsuperscript{13} What this means is that classificatory success is not value-free.

\textit{Lesson 2.} A second lesson from Dazy’s case concerns pluralism in terms of strategies or approaches, and pluralism concerning different cancer kinds. It is worth noting that the molecular-clinical approach to cancer defended here embodies a pluralism about cancer, rather than a monistic one insofar as cancers classifications are judged by their corresponding successful therapies. It is here I return to a worry, while not insurmountable certainly serves as an undercurrent driving this paper. Specifically, it is not yet clear how evolutionary approaches in philosophy of cancer might translate to clinical practice and scientific success. One consequence of modelling cancer progression according to evolution by selection is how cancer is construed as a somewhat singular functional phenomenon. Under an evolutionary framework, cancer progression is framed by natural selection at work where cancer cells are individuals in cell populations that adapt and evolve, respectively. Similarities among cancers in terms of their evolutionary dynamics are important here because they unify cancers by their shared functional properties. To identify functional commonalities across different cancer types—sometimes known as the ‘hallmarks of cancer’—is not necessarily wrongheaded because it shows why different cancer types are grouped together under one disease class. So, while there may be molecular heterogeneity within and across populations of cancer cells, perhaps there are shared dynamics of interactions between cells. That move by evolutionists is charged by their concern of molecular or “biomarker” approaches to cancer.

\textsuperscript{13} Advocating for less invasive diagnostic methods and technologies in early onset of disease was a strong theme at \textit{Revolutions in Diagnostics Symposium} (2018).
Liu (2018, 231-232) criticizes the biomarker approach for its insufficiency: there are methodological barriers such that the biomarker approach fails to capture cancer’s complex causal dynamics. A main goal of biomarker approaches is to identify the molecular mechanism(s) in order to intervene and change it. However, the dynamics in cancer progression, particularly in cancers with heterogenous profiles, are more complex than can be handled. There are many cancers that do not behave as the on/off switch presupposed by molecular cataloguing.

In response, I worry that evolutionists commit the very same crime, but without the amount of specificity and success mutation-tracking has had for constructing targeted therapies. Evolutionary models provide a functional gloss: cancer cells take up the roles of organisms or individuals in particular views of evolution that prioritize natural selection as a primary driver of change. If it is indeed an aim to identify shared dynamics, i.e. detrimental interactions between cells, adaptive traits passed through populations of cells, etc. in order to halt those processes in one swift motion, then the molecular on/off switch metaphor is merely replaced with the act of pulling an electrical plug out of the wall.

In order to reveal shared functional dynamics and interactions among heterogenous populations of cancer cells, arguably evolutionary thinking has the potential to gloss over salient molecular differences leading the charge in current clinical successes where targeted treatments take priority. Dazy’s case serves as a working example of how the molecular approach explains the guidance medical classification practices provide for numerous sorts of therapeutic interventions. Cancer diversity matters: A molecular approach foregrounds the plurality of cancer kinds. This does not mean that anything goes concerning classificatory
schemes—clinical success will (and should) constrain the viability of certain classifications and
classificatory programs. Assuming an evolutionary lens tends to group cancers together
functionally, there are certainly limits on how far that methodology can take us when clinical
success can sometimes tell a different story. Dazy’s case matters because it demonstrates how
cancer is not a one-size-fits-all disease, but a call for more precise, targeted therapies. Tracking
medical interventions that target cancer kinds brings us closer to the decisions and practices
tailored to the individual patient, as well as closer to the patient’s experience of that decision-
making process. This does not preclude interventions on cancer dynamics, but emphasizes the
track record of molecular work on biomarkers.

One might object that different structures can evolve to satisfy similar functions and so the
functional type-casting, which focuses on similarities among cancers, shows promise.
Functional similarities would be cancer cells with different biomarkers that fulfill the same role
in evolutionary models as objects of natural selection or bearers of adaptations, for example.
The idea is that we can (or should) target the overall function (i.e. evolutionary interactions)
instead of multiple structural (i.e. molecular) differences. However, recognizing cancer’s
structural diversity—i.e. the mutational complexity driving these classifications—has real
practical significance. And so, I propose a challenge to evolutionary theorists: what difference
does the evolutionary approach make to the experience of cancer as a disease both on the part
of the clinician and the patient?14 How will treating cancer as a singular functional class
translate to clinical therapy? What does it mean to intervene on process dynamics? While these

14 As Liu (2018, 233) admits, “investigating cancer through a Darwinian lens can lead to better
uses of existing treatments. However, this approach yields little mechanistic information that is
relevant for the development of new treatments (e.g. new drugs).”
questions are not necessarily insurmountable, they provide a much-needed challenge to evolutionary theorists: we can be pluralists about both scientific and humanities approaches and methodologies in cancer research. However, I contend that evolutionists working on cancer need to be clearer on what motivates their work, exactly how that translates to scientific practice, and at what cost given that assessing evolutionary dynamics entails targeting later stages of disease with higher mortality rates.

To take a line inspired by William James, cancer is a living practical affair and the molecular approach clearly answers the questions posed above. The philosophical relevance of classification practices (or any other scientific practice for that matter) can be motivated by explaining medical (or generally scientific) success. In the present case, foregrounding the structural plurality of cancer kinds is increasing our ability to treat the disease.

Lesson 3. And finally, recognizing a plurality of cancers shows how evolution by selection is not the only avenue to biological ontology. Cancer’s ontological plurality, however, need not be underwritten by realism concerning what cancer classifications capture. One might be tempted to motivate the focus on classifying cancer kinds from a realist position. That is, it might be tempting to argue that the structural plurality falling out of cancer classification is important because we’re getting at natural or ‘real’ divisions that exist among cancers independent of classifiers. A realist might say something like the following: The molecular classification scheme drawing from a molecular basis discussed throughout this paper provides a correct taxonomy of cancers that maps natural divisions among different cancer types. And so, that is why structural diversity trumps functional similarity (i.e. how the cells fulfill their roles when interacting with
one another) in this case. However, an unambiguously accurate taxonomy of cancers carries connotations of clear-cut boundaries, and that is not what science tells us.

In section 2.3 I outlined the complexity with which mutational processes generate signatures or patterns, which sometimes messily cross-classify cancer types. There is not some single (set of) essential mutation(s) that carve the boundaries of one cancer from another. Importantly, what science tells us about the world will in part depend on how we think science works. And as Ereshefsky (2016) argues, scientists have different epistemic and pragmatic reasons for positing classifications. So, there might be different reasons for classifying a cancer one way rather than another. And if we think about classification schemes in the medical context as tools for treatment, then tracking structural properties—i.e. mutational properties—makes those tools useful. By that token, classification schemes driven by treatment success lends itself to a context-sensitive plurality guided and constrained by different treatment avenues, such as the coarse-grained chemotherapy available for many different cancers compared to the targeted inhibitor therapy in Dazy’s case.

Specifically, I envision something similar to Joyce Havstad’s work on biochemical classification applied in the context of cancer: no single classification system will likely capture all structural properties of cancers (or functional properties for that matter); each picks out a limited set of candidates to work with, and those sets can be chosen based on the goals one has in employing that classification. In this case, if early detection and targeted therapy are the...
goals from a clinical point of view, then the molecular approach (at least for now) fits the bill. We can be good pluralists about cancer classifications even when diverse structural rather than broadly united functional properties do the heavy lifting. There may be countless, legitimate objectively-grounded ways of classifying the cancerous behaviour of cells (a la Dupre 1992, 18). Albeit, stochastically devised classifications are messy, but to impose some sort of order understandable to us need not only rely on functional gloss. Different classificatory schemes can be “piecemeal extension[s] of knowledge,” and that plurality acknowledges the diversity of cancer cases (see Dupre 1992, 18-19). Embracing that diversity is not only important for targeting treatment, but also for how treatment of cancer is portrayed to the public: not all cancers are an immediate death sentence, nor is it likely that one single cure will be found. Type-casting cancer as a broad functional class makes it seem as if we need to overcome a veil of variability by revealing a single (set of) fundamental and constant values. Against this, I maintain that individual cancer cases are not merely some amalgamation of interfering forces hindering a “natural” common expression or state of cancer yet to be uncovered. Along the lines of Havstad’s work, we’re empowered here to remain selective about classificatory programs on a contextual basis, and in the case of cancer we’re constrained by detection and treatment aims, as well as the epistemic and non-epistemic values discussed above that help those aims take shape.

And so, to do some biological ontology concerning cancer does not entail realist commitments. The molecular-clinical account I’ve advocated for here centers around classifications as tools for intervention success, which does not turn on whether cancer classifications are straightforwardly tracking some part of the world in a realist fashion. This is
partly reflected by social dimensions of cancer research in the sense of how clinical environments influence what counts as an appropriate outcome of classification practice. That a plurality of classificatory schemes can track intervention aims doesn’t mean anything goes concerning the epistemic standards that govern those choices: the world can push back concerning which detection technologies and therapies are successful relative to the intended outcome. Regardless, cancer classification is neither about exposing some pre-existing order nor does it mean that good classifications are merely what the classifiers say are good—sorting good from bad classificatory schemes is constrained by what works (in this case) therapeutically. While the ontologies read off these classifications may vary, the driving point for our final lesson here is a non-evolutionary avenue to biological ontologies.

In summary, I have defended molecular approaches to cancer: attention to mutational process and pattern in cancer classification explains clinical success despite its rather unfashionable status among philosophers of biology and medicine. I introduced somatic mutation theory (SMT) as an entry point for discussing the role of intrinsic cellular features in cancer classification and why mutations matter for distinguishing among cancer kinds. These mutations mattered for the clinical decision-making process that determined medical intervention for Dazy’s case. I primarily focused on advantages of the molecular approach to cancer, how it shapes the classificatory and epistemic practices of cancer biology, and emphasized that structural diversity in cancer classifications yields tools for intervention and positive clinical outcomes in medicine.
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