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Convergent Evolution, Evolving Evolvability, and the Origins of Lethal Cancer

Kenneth J. Pienta[1], Emma U. Hammarlund[2,3], Robert Axelrod[4], Sarah R. Amend[1], and Joel S. Brown[5]

ABSTRACT

Advances in curative treatment to remove the primary tumor have increased survival of localized cancers for most solid tumor types, yet cancers that have spread are typically incurable and account for >90% of cancer-related deaths. Metastatic disease remains incurable because, somehow, tumors evolve resistance to all known compounds, including therapies. In all of these incurable patients, *de novo* lethal cancer evolves capacities for both metastasis and resistance. Therefore, cancers in different patients appear to follow the same eco-evolutionary path that independently manifests in affected patients. This convergent outcome, that always includes the ability to metastasize and exhibit resistance, demands an explanation beyond the slow and steady accrual of stochastic mutations. The common denominator may be that cancer starts as a speciation event when a unicellular protist breaks away from its multicellular host and initiates a cancer clade within the patient. As the cancer cells speciate and diversify further, some evolve the capacity to evolve: evolvability. Evolvability becomes a heritable trait that influences the available variation of other phenotypes that can then be acted upon by natural selection. Evolving evolvability may be an adaptation for cancer cells. By generating and maintaining considerable heritable variation, the cancer clade can, with high certainty, serendipitously produce cells resistant to therapy and cells capable of metastasizing. Understanding that cancer cells can swiftly evolve responses to novel and varied stressors create opportunities for adaptive therapy, double-bind therapies, and extinction therapies; all involving strategic decision making that steers and anticipates the convergent coevolutionary responses of the cancers.

Introduction

Nearly 10 million people worldwide and more than 600,000 in the United States die from cancer yearly, the equivalent of 1,600 deaths every day (1, 2). By 2040, estimates predict 16 million annual cancer-specific deaths globally (3). Although advances in curative treatment (i.e., surgery and radiation to remove the primary tumor) have increased survival of truly localized cancers by up to 90% in the United States for most solid tumor types, cancers that have spread are typically incurable (2). Cancer that has metastasized accounts for more than 90% of cancer-related deaths (3). Metastatic disease remains incurable because, somehow, tumors evolve resistance to all known natural and synthetic compounds, including anticancer therapies (4–13).

The Lethality of Cancer and Convergent Evolution

From a therapeutic point of view, cancer exists in two forms, curable and incurable. Approximately 50% of all cancers are cured by surgery or radiation that eradicates the primary tumor. However, in the other 50% of patients, definitive treatment of the primary cancer does not eradicate the disease (**Fig. 1**). What is the difference between curable and incurable disease? It is not simply the size of the tumor. The incurability and lethality of cancer is based on two fundamental properties: cancer cells can spread throughout the body (metastasize) and they evolve resistance to all known therapies (13–15). If a cancer does not spread, it simply exists at a single site (e.g., a lipoma, an adenoma, and many adenocarcinomas can be successfully excised for cure). If a cancer is not resistant or too slow to evolve resistance, it can be cured by systemic therapeutic interventions (e.g., testicular cancer). Cancers that are curable either do not have the capacity, the cell numbers, or the time to evolve resistance. It must be noted that each independent origin of incurable cancer develops capacities for both metastasizing and evolving resistance. Each of the nearly 10 million people dying from cancer every year developed that lethal cancer *de novo*. Therefore, cancers in different patients appear to follow the same core eco-evolutionary program that manifests independently in the affected patients. Between patients, this repeatedly leads to the convergent and parallel evolution of metastatic potential and resistance (**Fig. 1**). Together, these convergent eco-evolutionary dynamics render the disease incurable and lethal in virtually all metastatic patients. Such convergent reproducibility across patients requires an explanation beyond the slow and steady accrual of stochastic mutations. The common denominator may be that cancer cells evolve the capacity to evolve, that is, evolvability.

Evolvability represents a trait by which the generation of heritable phenotypic variation itself becomes heritable and subject to natural selection (**Box 1**). Evolving evolvability may be an adaptation for cancer cells to produce random mutations in all or parts of the genome, heritable epigenetic changes, chromosomal rearrangements, and increased phenotypic plasticity as a means for evolving more quickly to sudden catastrophic changes in their microenvironment. The mechanisms for generating increased heritable variation will include processes quite unlike the classical mutations of alleles within a biological system characterized by Mendelian genetics. In cancer, natural selection operating on the system of inheritance would speed

[1]The Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, Maryland. [2]Nordic Center for Earth Evolution, University of Southern Denmark, Odense, Denmark. [3]Translational Cancer Research, Department of Laboratory Medicine, Lund University, Lund, Sweden. [4]Gerald R. Ford School of Public Policy, University of Michigan, Ann Arbor, Michigan. [5]Cancer Biology and Evolution Program and Department of Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida.

Corresponding Author: Kenneth J. Pienta, The James Buchanan Brady Urological Institute at the Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287. Phone: 410-502-3136; Fax: 410-955-0833; E-mail: kpienta1@jhmi.edu

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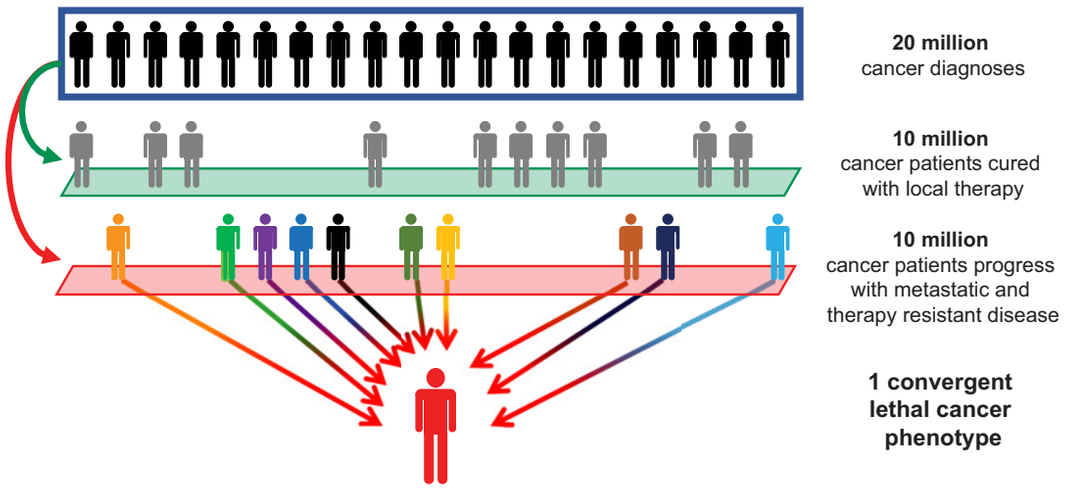

Figure 1.
The convergent evolution of lethal cancer. Each year worldwide, 20 million people are diagnosed with cancer. Approximately 10 million of those patients are cured of their disease by local therapy. The other 10 million patients develop lethal and incurable disease. Each of these 10 million cancers in different patients lead to the same convergent phenotype: metastatic potential and therapy resistance.

the rate at which natural selection drives other phenotypic traits associated with the survival and proliferation of cells. Nature is replete with examples in which organisms from bacteria to protists to metazoans have evolved evolvability, allowing evolutionary shortcuts. While evolvability among bacteria has led to biochemic diversity, in metazoans it has led to a diversity of morphologies. That natural selection might evolve its own tempo and mode of evolution may at first glance seem befuddling, but it is increasingly recognized as important for cancer evolution (16–21). We hypothesize that evolvability itself is a key adaptation common to virtually all cancers across all patients. It likely explains metastases and the evolution of resistance.

Evolutionists have debated and speculated on what would happen if 10 million earths each provided an independent experiment into the evolution of life from the same initial conditions (22–25). While there is much disagreement on whether the "tape of life" would replay the same way, most agree that, along the evolutionary tape of animals, the broad patterns of speciation and analogous adaptations, such as sensory systems like eyes or teeth to aid prey capture and digestion, would repeat. Biological adaptations are the result of ecological stresses and depend on specific genetic, physiologic, and morphologic response mechanisms. For instance, eyes in humans and squid function similarly, with a lens and retina, but have different origins and development. They are considered analogous traits resulting from convergent evolution (**Box 1**). Both deer and kangaroos successfully crop grass, sprigs, and leaves but through different means. Each has independently evolved a knife and chopping block technique. In deer, the upper pallet provides the chopping block and lower incisors the knife. In kangaroos, upper incisors provide the knife and their two remaining lower incisors jut straight out to form the chopping block. Determinism and contingency in natural selection combine to produce convergent evolution. Regrettably, each patient represents an independent earth in terms of the origin and progression of a new cancer clade.

The "tape of tissue transformation" replayed across several million patients gives insights about the reproducibility of evolutionary patterns. The unique cancer in each of the 10 million patients that die yearly has evolved from an origin of nearly the same genetic material (normal human cells). Similarly, new species can arise from a common ancestor in nature. In a system of caves in Mexico, speciation of cave fish has occurred from the same river-dwelling progenitor species. Each cave is like a "patient" that evolves a cave fish *de novo* from the same genetic stock. The separate populations of cave fish converge on similar phenotypes, yet each is different at the details of genetic and molecular machinery. The evolutionary paths of cave fish populations involve mutating and tweaking existing genomes and developmental pathways. Very few truly novel genetic innovations occur. Although different at the genetic level, the cave fish populations arrive at the same remarkable phenotype of no eyes and no skin pigments (26–28). Cancers derive from fundamentally the same genome, and while demonstrating significantly different evolutionary potential, the cancers of different patients converge on similar phenotypes and tumor properties. The differences of evolutionary potential between cancers arise for two reasons. First, individual cancers have dramatically different environmental selection forces. Second, during development the specialization of tissues involves placing epigenetic straightjackets on cassettes of genes to ensure that cells of different tissues "breed" true. In contrast, "stem" cells represent stages where fewer constraints are in place and this stemness is hierarchical going back to the blastula. An early straitjacket canalizes cell lineages into the germ layers of endo-, meso-, and ectoderm, and canalizations continue to cascade along each cell lineage imposing additional restraints. Much progressive evolution by cancer cells involves simply unlocking these cassettes. The tissue origin of metastasizing cancers remains detectable, similar to how animals, plants, and fungi can be phylogenetically traced back to a last common eukaryotic ancestor. Despite the lineage-specific unlocking of cassettes and tissue-specific selection forces, lethal cancers all converge on the properties of metastasis and resistance.

The origins of the metastatic process and the development of therapeutic resistance are often perceived and treated as separate and distinct phenomena, as well as usually studied by different groups of people. The subdisciplines of the study of metastases and therapeutic resistance, therefore, have largely developed independent of each other. Metastasis by one or several cancer cells of a primary (or secondary) tumor is widely considered to be a stochastic event (14). The sequential steps of the metastatic cascade describe functional cellular requirements that must be acquired to survive the environmental selection pressures of each stage (1, 14, 29–32). Like the spread

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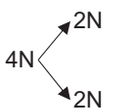
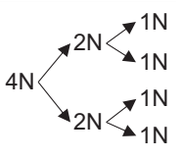
Box 1. Terms and definitions.

Term	Definition
Organism	An individual animal, plant, fungus, or single-celled life form capable of reproduction, growth and development, maintenance, and reaction to stimuli. For our purposes, it represents a unit of natural selection distinguished from *components* of an organism such as organelles, cells, or organs. We see cancer cells as organisms.
Species	The lowest level of taxonomic classification. The biological species defines a species as those organisms with the ability to interbreed and produce fertile offspring. In defining species of cancer within a patient's tumor(s), we are subscribing most closely to the ecological species concept defined by those organisms that are genetically and phenotypically similar and that possess shared adaptations for filling a particular ecological niche or niches. We see a cancer species' integrity as being maintained by natural selection.
Clade	A group of organisms that all evolved from a single common ancestor. Each patient's cancer represents a novel clade of cancer cells.
Hyperspeciation	Multiple speciation events from a common ancestor compressed into a relatively short amount of time. Unicellular and multicellular organisms both demonstrate the ability to speciate rapidly, e.g., during cancer progression or the adaptive radiation of animals following mass extinctions.
Cambrian explosion	First diversification event of animals on Earth. The sudden and global occurrence of worm tracks define the start of the Cambrian Period 543 million years ago (Ma) and the Eon of visible life (Phanerozoic). The event dramatically saw the evolution of most modern Animal Phyla within a short geologic timeframe (550–520 Ma).
Convergent evolution	Independent evolution of similar (termed analogous) adaptations in unrelated species or clades. For our purposes, this can represent the similar adaptations that occur in the cancer clades of different patients.
Evolvability	The capacity to evolve; a trait that influences the *generation* of heritable phenotypic variation become subject to natural selection.
Protist/Protozoa	A eukaryotic (and typically unicellular) organism that is neither animal, plant, nor fungus. We see cancer as the evolution of a new protist that speciates from its animal host.
Metazoans	Multicellular organisms, synonymous with the eukaryotic kingdom Animalia, consisting of the Phylum Porifera (sponges) and Subkingdom Eumetazoa (all other animals). Metazoans are multicellular, oxygen consuming, heterotrophic organisms that (generally) grow from a blastula during development, are motile at some stage, and reproduce sexually.
Mitosis	Cell division of a single cell that results in two daughter cells with the same number of chromosomes as the parent. Four stages: prophase, metaphase, anaphase, and telophase, followed by cytokinesis. 
Meiosis	Cell division of a single cell that results in four daughter cells with half the number of chromosomes as the parent (typical of gamete production). Two stages: Meiosis I results in two daughter cells with the identical number of chromosomes as the parent. Meiosis II results in four daughter cells with half the number of chromosomes as the parent. 
Aneuploid	The duplication (in whole or in part) of one or more, but not all, chromosomes.
Polyploid	A whole-number duplication of a cell's genomic material. Generally associated with a duplication of all chromosomes.
Poly-Aneuploid Cancer Cells (PACCs)	Aneuploid cancer cells that have duplicated their entire genome resulting in a cell that is polyploid and aneuploid. Also referenced in the literature as polyploid giant cancer cells, multinucleated giant cancer cells, blastomere-like cancer cells, osteoclast-like cancer cells, and pleomorphic cancer cells.

of an invasive species in nature (nearly impossible to eradicate or reverse), the cancer cells must enter the blood stream (intravasate), circulate (disperse), colonize (extravasate), and establish a viable population at a distant site or organ. Of the billions of cancer cells shed from the tumor, only a rare subset survives to succeed at a distant site (14). Such cells are those that are genetically or phenotypically primed to survive the metastatic cascade. Similarly, therapeutic resistance classically is attributed to stochastic genetic mutation resulting in high tumor cell heterogeneity. By this rationale, within the billions of cancer cells in a tumor, resistance to therapies develops by random chance and, when treated, sensitive cells die, while the resistant few survive and emerge as the dominant clone after treatment (4, 33–38). The two properties of metastasis and resistance that lead to cancer lethality are rarely considered as emerging from a common process. From an eco-evolutionary perspective, the two properties of metastasis and therapy resistance seem to go hand in hand, suggesting a link between these two properties of cancer's resilience.

The Lethality of Cancer and Hyperspeciation

A tumor results from a cascade of cell divisions that generates billions of cancer cells. A cancer becomes increasingly lethal when

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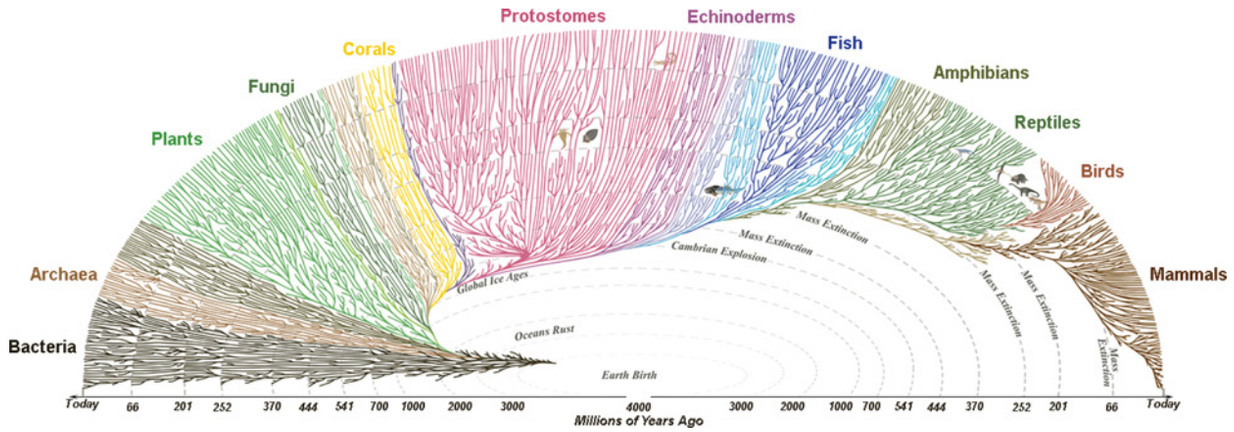

Figure 2.

The diversification of species. The tree of life diagram shows the major extant branches of life across a geologic time scale of millions of years. Major clades (distinctly colored) are related by a last common ancestor. Species are represented by branch lines within these clades. Dashed lines indicate major points of speciation (e.g., the Cambrian Explosion approximately 543 Ma) and extinction, emphasizing the changes in diversity throughout the history of life. (Figure modified from and used with permission: © Leonard Eisenberg, 2008, 2017, All Rights Reserved. https://www.evogeneao.com).

cancer cells successfully abandon their original context, migrate and evolve into new tissues and habitats, and forge novel evolutionary paths. This evolutionary arc toward lethality requires a continual supply of heritable variation as fuel for natural selection. The necessary genetic perturbations for this to happen reside within the cancer hallmark of genetic instability. Diverse sources of chromosomal, genetic, and epigenetic mutations coupled to changing environmental pressures, and migration can all represent classic components of Darwinian evolutionary dynamics (39–43). The field of cancer evolutionary dynamics has traditionally focused on describing how cancer clones evolve over time, acquiring characteristics that convey survival advantages. But the implications of cancer's evolved capacity for rapid evolution to novel circumstances combined with diverse sources of intra- and intertumoral heterogeneity to drive hyperspeciation within a patient's cancer clade remain elusive.

It has been documented in the cancer biology literature that the malignant transformation of a cell into cancer is a speciation event, subject to the laws of natural selection (39). In unicellular eukaryotes, a species is defined by genetic separation and phenotypic differentiation. Because cancer cells have altered genomes as well as observable physical differences, distinct from each other and from normal human cells, both cancer initiation and the continued speciation events

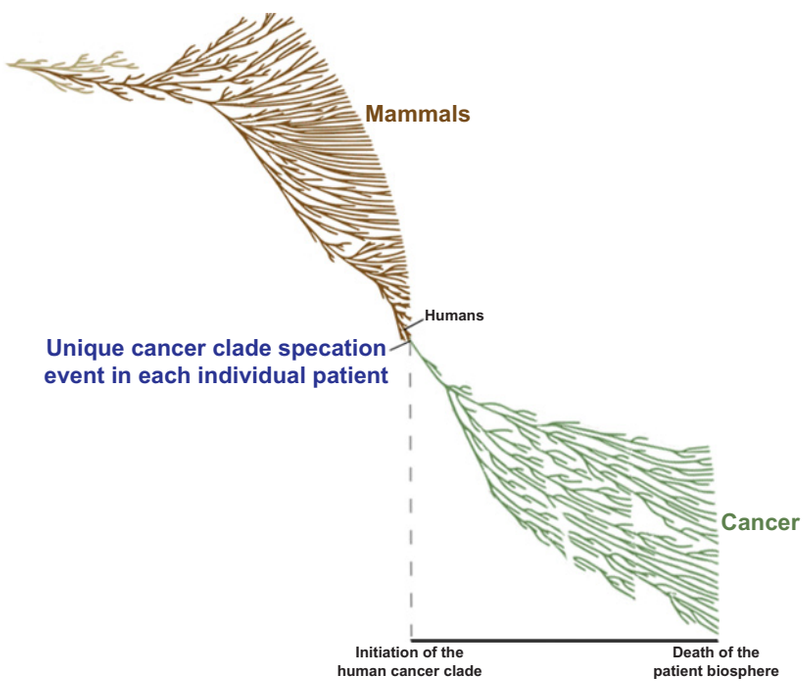

Figure 3.

The diversification of cancer species within a monophyletic clade. The cancer clade arises from a common ancestor: the single-cell cancer protist. After this initial speciation event, the species rapidly diversifies into multiple species, thus generating a monophyletic cancer clade. The various species within this clade will experience changing ecological pressures during cancer progression and treatment, resulting in additional speciation and extinction events. Ultimately, the cancer clade only goes extinct upon the death of the patient: the elimination of its requisite biosphere. (Figure modified from and used with permission: © Leonard Eisenberg, 2008, 2017, All Rights Reserved. https://www.evogeneao.com).

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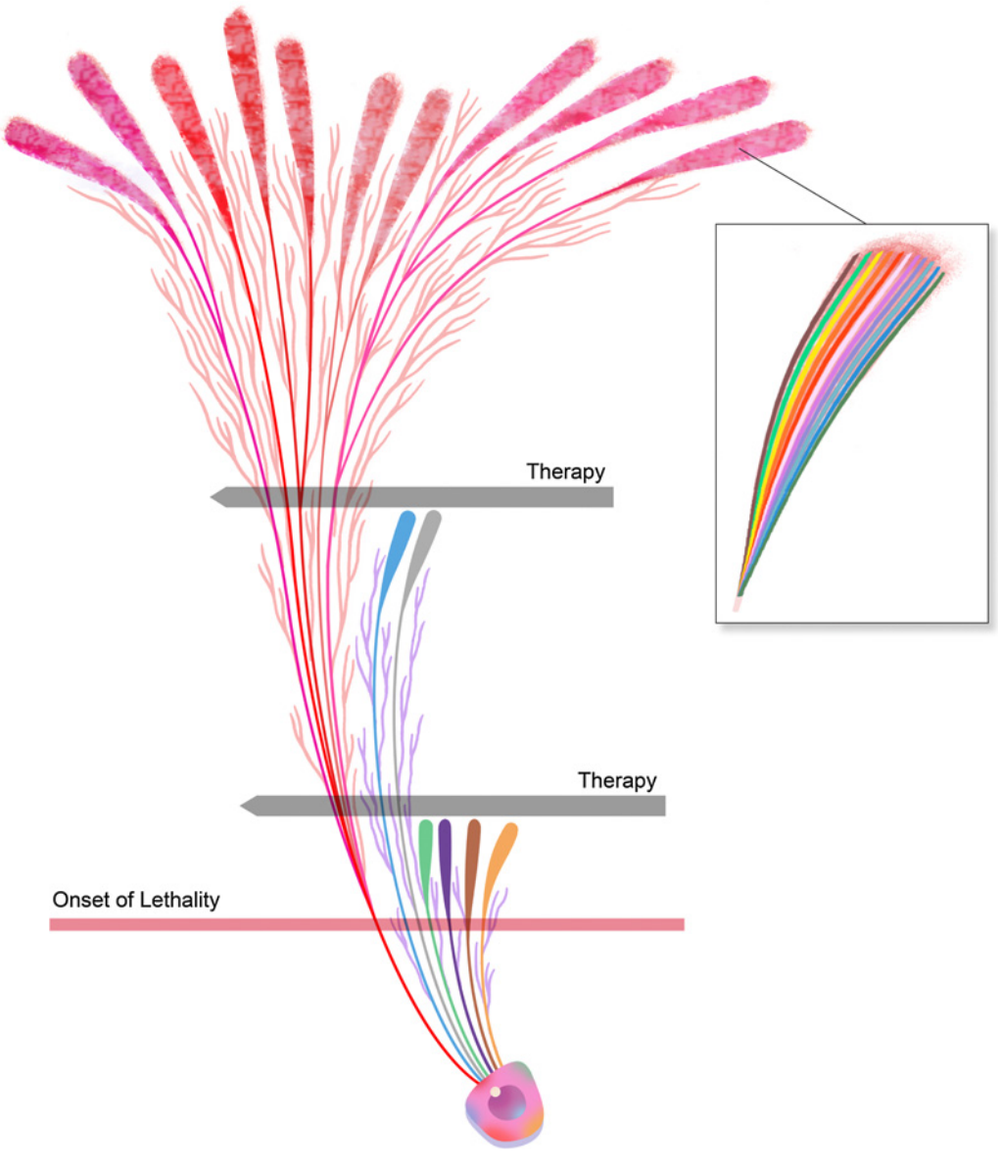

Figure 4.

Evolution of evolvability in species of the cancer clade. All cancer species arise from a single unicellular cancer protist followed by rapid hyperspeciation. In this diagram, each line/branch represent a genetically distinct cancer species, all related to the same common ancestor. Within each species, there may emerge multiple different strains, each with different epigenetic variation and carrier mutation status that arise in response to varied ecological circumstances (inset). There is strong selection for evolvability as successful cancer cell species are likely those that respond to selection pressures in the tumor microenvironment. Tumor heterogeneity promotes an adaptive radiation of the cancer cells into distinct species that occupy the different ecological niches. Thus, even as nonevolvable species are eliminated by therapy, those species that evolved an evolvable phenotype survive to seed a metastasis and mediate therapy resistance (in this diagram, the pink species). The selection for this evolvable phenotype – and therefore the lethal phenotype – is initiated early in cancer progression, prior to any exposure to therapy. (Illustrations: Tim Phelps © 2019 JHU AAM; Department of Art as Applied to Medicine; The Johns Hopkins University School of Medicine).

apparent as the disease progresses can be recognized as a speciation process. A new cancer clade arises when a cell that had previously been a component part of the human multicellular organism transforms into a new unicellular organism, a cancer protist that now inhabits but is distinct from the human patient (44–47). A protist is a predominantly unicellular eukaryotic organism that is neither an animal, land plant, nor true fungus. The cell's jump from being part of the whole organism's program to being its own distinct unit of selection clearly qualifies as a speciation event. By all species concepts, a purely unicellular organism is distinct from a purely multicellular one; even if the unicellular organism's ancestor was multicellular. The cancer is now its own independently evolving lineage.

As the population size of this cancer protist grows, its tumor ecosystem expands in size and heterogeneity. The novel heterogeneity produces disruptive and diversifying selection that further propels speciation whereby different cancer cell species emerge that specialize in exploiting particular opportunities, avoiding particular hazards, or both (48). To clarify our terminology, we see each patient's cancer as a

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cancer clade distinct in origin from that in other patients. A patient with cancer has a single clade of cancer cells, unless cancer has independently arisen more than once in that patient. When separately evolving lineages of cancer cells within a patient (metapopulations) diverge in both their heritable phenotypes and ecologies, we see this as a speciation event in which the cancer clade diversifies (**Box 1**). This definition for cancer species within a patient does not conform to the biological species concept of populations of actually or potentially interbreeding individuals. It does conform to the ecological or strategy species concept typically applied to protist species (49).

To describe cancer as simply a new species occupying its patient biosphere is therefore insufficient. The diverse and numerous cancer species inhabiting the patient are members of a single monophyletic clade arising from a single common ancestor: the initial cancer protist. All life on Earth emerged from a common ancestor and, across geologic time, distinct clades populated by many distinct species emerged (**Fig. 2**). A clade is a monophyletic group that is made up of a single common ancestor and all of its resulting descendant species. For example, a sparrow and an ostrich are both members of the bird clade (class Aves), while dogs and mice are both members of the mammal clade (class Mammalia; **Fig. 2**). Within a single species there can exist many different strains. In dogs (species *Canis lupus familiaris*), there exist strains (or breeds) as divergent as a Pomeranian and a Border Collie. The mouse strains familiar to researchers such as C57BL/6 and BALB/c are all of the same species: *Mus musculus*. Similarly, while cancer initiates as a single species in a patient, it rapidly diversifies into multiple species that all form a single monophyletic clade. These cancer species are genetically distinct and are defined by irreversible and distinct genetic characteristics, such as particular driver mutations and chromosomal rearrangements that are inherited by future generations within that species (**Fig. 3**). Each of these species, however, may contain a myriad of phenotypically distinct strains with different epigenetic variation and carrier mutation status that arise in response to varied ecological circumstances within and between tumors (**Fig. 4**).

Charles Darwin noted the importance of thinking about evolution in terms of species and clades. The field of cancer evolutionary biology generally considers cancer as a new species with tumor cell heterogeneity described as clones or subclones. It may be more appropriate to consider tumor cell heterogeneity as the diversification of cancer species within a cancer clade. Observed tumor cell heterogeneity, therefore, is likely the result of both the diversification of many genetically distinct cancer species (what has previously been characterized as clonal variants with distinct driver mutations within a single species) and the intraspecies variation of multiple different cancer strains within a single species, each with different survival advantages and adaptations to the dynamic ecology of a tumor ecosystems.

The speciation of cancer cells within the cancer protist clade can be described in a series of "steps" (**Fig. 4**; refs. 44, 46). Step 1 is the initial transition event from the multicellular metazoan "ancestor" into a unicellular cancer protist where the progenitor host of this cancer becomes the new protist's entire biosphere (50). The cancer as a new unicellular organism has high evolutionary potential in that its initial characteristics are far from an evolutionary optimum or peak on its adaptive landscape (51). Step 2, there is strong selection for evolvability as a successful cancer cell species will often be the one that can most rapidly respond to new selection pressures, for example, lack of nutrients in the environment or therapeutic stress. Step 3, tumor heterogeneity, whether inherent or generated by the actions of the cancer cells themselves, promotes an adaptive radiation of the cancer cells into distinct species and intraspecies strains that occupy the different ecological niches offered by heterogeneous environments. Step 4, if there are successful metastases, for many untreated cancers this is a matter of when and not if, steps 2 and 3 repeats. In the case of metastases, the successful colonizer likely has evolvability as a pre-existing adaptation and it may be preadapted to many of the conditions in the new organ (i.e., the mechanism behind Paget's seed and soil hypothesis: a cell "regarded as an organism, alive, and capable of development"; refs. 14, 29, 30). From step 3 onwards the evolvability itself is under selection and, thus, evolving within the separate cancer species.

It has been noted that a high diversity of cancer cell subtypes appears very quickly in oncogenesis. In the guise of the "big bang" theory of clonal expansion, it has been suggested that this variability is largely independent of natural selection or subjected to only weak selection (52–54). That may be. But, as visible extant heritable variation, it is equally likely that natural selection has already exerted strong disruptive selection. In this case, the rapid diversification of cancer cell types resembles the first event of animal diversification, or hyperspeciation, on Earth called the "Cambrian explosion." The cancer Cambrian explosion may be regarded as a phase of hyperspeciation (**Figs. 3** and **4**; **Box 1**). The eco-evolutionary feedbacks between tumor heterogeneity and novel evolvable traits generate opportunities for diverse specialist cancer species. The Cambrian explosion of animals occurred during a geologically brief period in time some half a billion years ago when most Phyla diversified (**Fig. 2**; refs. 55–57). In addition to environmental changes and heterogeneity, developmental studies suggest that animals were evolving more refined regulatory mechanisms for the development of specialized tissues. This likely involved the channeling of the fates of cells via cassettes of genes that could be epigenetically imposed and released. This flexibility, whereby small epigenetic changes could direct tissue specialization within an organism, also enhanced evolvability of whole populations, and the rapid diversification of primitive animals (58, 59). The dramatic diversification and adaptive radiation of cancer cells during oncogenesis and animal species during the Cambrian can be regarded as hyperspeciation. Furthermore, the capacity for small epigenetic changes to have large phenotypic consequences for the cell likely carries over into cancer cells with profound consequences for hyperspeciation within the cancer clade and dire consequences for the patient.

In cancer, daughter cells inherit the genetic background of the parental cell, like begets like, but with some genetic and epigenetic mutations. This heritable variation gives rise to multiple strains within a single cancer species and provides the fuel for natural selection to respond to novel and often dynamic environmental conditions (**Fig. 4**; refs. 33–43, 50). The division of cells over space and time leads to observable tumor cell heterogeneity across the billions of cancer cells within a tumor. It has been suggested and generally believed that resistance to therapies develops by random chance, making some cancer cells resistant to a particular therapy. When a patient's cancer is treated with chemotherapy, many cells die, but the resistant ones have a Darwinian evolutionary advantage and proliferate, repopulating a now-resistant tumor (4, 33– 38). This idea finds a parallel in the field of extinction ecology where it has been noted that a very large population can be resistant to extinction from catastrophic environmental changes (60–62). This resistance is mediated via a "rescue effect" whereby the population is so large that upon the change in environment there are already mutants in the population (intrinsic resistance) or there is sufficient time and numbers to generate mutations (adaptive resistance) that will rescue the population from extinction (60–62).

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The Evolution of Evolvability

Cancer as a species, a single-cell protist, provides a useful first step in understanding the lethality of cancer. In evolutionary terms, speciation occurs when groups in a species become reproductively isolated and diverge. Because each generation of cancer cells is reproductively isolated from the prior generation, each progeny cell has the potential to diverge evolutionarily not only into a new daughter cell but perhaps give rise to a new species that exploits a different ecological opportunity within the tumor. From an evolutionary standpoint, a successful cancer inhabiting the patient starts as a single cell and then rapidly diversifies into novel and distinct cancer species (44–47). Intrinsic genetic instability in combination with natural selection as a result of environmental stressors leads to accelerated evolution and speciation events (hyperspeciation) across the cancer's (and the patient's) lifetime (refs. 50, 57; **Fig. 4**). Furthermore, motility as a trait propels speciation as cancer cells occupy new and spatially separate tumor habitats. Hence, the collection of cancer cells that is manifested as tumor cell heterogeneity consists of multiple distinct cancer cell species defined by distinct traits and ecologies. Given the diverse ecological opportunities that can be filled within a tumor, a cancer cell species that can evolve adaptations faster and achieve points of disruptive selection more quickly will outcompete and replace cancer cell species that evolve more slowly. The near certainty of a "Cambrian explosion" of cancer cells within a patient's primary tumor will favor evolvability as an adaption.

Evolvability, therefore, can be considered as a trait. According to Fisher Fundamental Theorem of Natural Selection, the rate of natural selection is proportional to the additive genetic variance (more generally, heritable variation that can be acted upon by natural selection) multiplied by the strength of selection (63, 64). Evolvability is a heritable trait that influences the amount of heritable variation. All else equal, a cancer species with higher evolvability will produce heritable variation more rapidly than one with less evolvability. If a species is at an evolutionary optimum and this optimum is stable, then heritable variation around this evolutionary peak will be negative or neutral. Natural selection should favor less, not more, heritable variation. On the other hand, imagine species that are far from their evolutionary optima, or that the constant changes to the environment shift the location of their evolutionary peaks. In this case, traits that generate rather than constrain heritable variation will be favored. Cancer initiation starts the cancer clade far from any peak; evolvability would be favored as a means for rapid evolution and replacement of less fit phenotypes by more fit ones. Once established as species, if cancer cells experience unpredictable, high amplitude changes to their tumor microenvironments, then traits for high evolvability will still be favored and retained as a means for evolutionary tracking.

Metastasis and Therapy Resistance as the Added Benefits of Evolvability

Evolvability as an adaptation may arise early within the cancer's clade. Early in their evolutionary history, it allows the cancer cells to more swiftly dispense with the normal-cell functions that contribute little or contribute negatively to the cancer cells' survival and proliferation rates. Furthermore, traits in the evolutionary luggage of the human genome could likely be uncovered that will propel progressive evolution of the newly originating protist. Both negative selection against existing normal-cell traits and positive selection for more successful protist traits will, all else equal, favor the cancer cell species that can evolve more quickly (63–65). Second, the opportunity to speciate in response to tumor microenvironment heterogeneity may provide a subsequent advantage (42, 48, 50). A rapidly evolving cancer cell lineage could exploit the opportunities provided by cancer's Cambrian explosion. This second advantage and its subsequent formation of diverse cancer species may be sufficient to render metastasis a near certainty rather than a mere possibility.

A third advantage of evolvability is evolutionary tracking and evolutionary rescue (60–62). These are endpoints of a continuum of responses. Evolutionary tracking permits heritable responses to gradual or catastrophic changes to the cancer cell's environment. Evolutionary rescue occurs when a species that would otherwise go extinct within the changed circumstances is able to evolve in a manner that permits it to recover and succeed. Traits associated with evolutionary tracking and evolutionary rescue create the convergent and parallel evolution of cancer cells toward metastasis and therapy resistance, respectively.

Cancer cells likely experience multiple catastrophes within their tumor environment driven by sudden bouts of fluctuating oxygen availability, redirections of angiogenesis, build-ups of toxic cell metabolites, sudden onsets of activated and antitumor immune cells, and sudden onsets of necrosis (14, 20, 32, 41, 42, 50). While natural selection cannot prepare a cancer cell for the particulars or eventualities that have not yet happened, it can select as a trait for preparedness to the likely occurrence of some sort of catastrophic event. The trait of evolvability can be just such an adaptation. As such, extravasating in distant tissue landscapes or being subjected to a novel therapeutic agent represent novel catastrophes, at least to the cancer cells. Being able to evolve quickly promotes success of the dispersing cancer cell and resistance to the surprise onset of a therapy. To be clear, dynamic phenotypic plasticity can help a cancer cell survive environmental changes in an immediate time frame (e.g., epigenetically driven epithelial-to-mesenchymal transition) but evolvability allows heritability across generations (12, 15, 34, 66). Metastasis and resistance become near certain sides of the same evolutionary trait, namely the capacity to adapt rapidly to novel changes. When a capacity to generate increased heritable phenotypic variation evolves in a population, that very capacity may allow the population to evolve rapidly, and thus survive in a range of subsequent novel settings. Both therapy resistance and metastasis may require (i) rapid evolutionary tracking, (ii) evolutionary rescue, and (iii) some preadaptations that might be present by virtue of having diverse coexisting cancer species. All three of these conditions become possible when cancer cells have evolved evolvability.

Traits that Confer Evolvability

In nature, sexual reproduction is one of the foremost means for generating heritable variation. One of the benefits to sex is the ability to evolve more rapidly in response to changing environments. The Solanaceae (family of plants containing tomatoes and nightshades) has species that can self-pollinate (selfing) and others that are obligate out-crossers (self-incompatible). Selfing has the advantage of guaranteeing that all of a plant's seeds get fertilized. Out-crossing guarantees greater genetic diversity among a plant's seeds and hence a greater capacity to evolve more rapidly in the face of perturbations or environmental change (67). It is therefore noteworthy that in the patterns of speciation and extinction for this family, selfing species never replace out-crossing species. Instead, out-crossing species often replace selfing species as well as giving rise to new out-crossing species (68). New selfing species only occur when an out-crossing species evolves selfing (69). Furthermore, in species such as the freshwater Cladoceran *Daphnia* (small crustaceans known as water fleas), asexual reproduction proceeds during the summer growing

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season and sexual reproduction happens when population densities are very high (intense competition) or as winter approaches and eggs must survive the winter (70). Asexual reproduction maximizes growth rates during the favorable times, and sexual reproduction maximizes heritable variation as lineages over-winter and prepare for the following spring (71, 72).

Bacteria and protists such as yeast exhibit several traits that increase heritable variation. In all of these cases higher rates of evolvability seem to be advantageous or facultatively occur during times of stress, environmental change, or during catastrophes. As an adaptation, evolvability can evolve (20, 73). In bacteria the mechanism can be as simple as increased mutation rates or DNA exchange (74, 75). Furthermore, in both yeast and bacteria the elevated rates of mutation may be localized to specific loci that have direct fitness consequences for various types of stresses repeatedly yet unpredictably encountered (76, 77). Elevated mutation rates on selected loci may create heritable variation when it is needed most, further accelerating evolutionary tracking and evolutionary rescue (21, 78). Yeasts have been shown to induce polyploidy and aneuploidy that accelerates the evolution of appropriate adaptations in response to stress (79). Surviving giant cells with increased genetic material revert to "normal" yeast following the stress, and their progeny retain adaptations for survival under the adverse conditions (80, 81).

A hallmark of cancer is genetic instability and this hallmark may be the result of cancer evolving evolvability as an adaptation. The mechanisms may be as diverse as seen in bacteria, yeast, and other protists. These can include elevated mutation rates, gene duplication, transposable elements, chromosomal rearrangements, aneuploidy, a form of sex via cancer cell fusions, and multinucleated cells (18, 21, 82–85). A particularly salient and perhaps dangerous adaptation by cancer cells may be the capacity to produce poly-aneuploid or polyploid giant cancer cells (refs. 86–90; **Box 1**). Recent work has identified several properties: (i) in those cancers examined, a small fraction of poly-aneuploid cancer cells (PACC) are present in the population, (ii) PACCs seem to be uniquely stress resistant and may represent a contingent strategy of many cancer species whereby 2N cells form PACCs with increased genomic content and increased size (often ~8 times bigger by volume) through aborted cytokinesis or cell–cell fusion, (iii) PACCs may allow for evolutionary rescue by accelerating the evolution of resistance and stress responses. The 2N progeny of PACCs often exhibit novel traits (e.g., therapeutic resistance) relative to the original 2N cells that gave rise to the PACCs (86–90). Any and all of the above mechanisms can generate heritable variation for natural selection; and likely play some role in metastasis and therapy resistance. In particular, PACCs may be the most pervasive and lethal means by which cancer cells evolve evolvability, ensuring both metastasis and therapy resistance, and rendering such cancers thus far incurable and lethal.

Targeting Evolvability

A number of authors have suggested the opportunity for therapies to slow the rate of evolution of cancer cells. In effect, this means targeting the means by which they generate heritable variation. This could either take the form of killing cells that exhibit a particular trait for generating heritable variation or by stunting the trait's ability to do so. In the former case, there would then be selection to overcome the targeted therapy, and in the latter case there would be selection for different traits that fulfill the task of generating heritable variation. Such approaches to therapy have merit. Even if they may not be entirely successful, they could illuminate the traits that confer evolvability. Simply being able to slow the evolvability of cancer would increase as well as prolong the efficacy of traditional therapies.

Therapeutic strategies could take advantage of cancer's ability to evolve rapidly. Adaptive therapy has been used to successfully delay the onset of therapeutic resistance to a single agent in castrate-resistant prostate cancer (91). The idea is that with a cost of resistance, more sensitive cancer cells will have a competitive advantage over resistant ones in the absence of therapy and vice-versa under therapy. Thus, therapy can reduce sensitive cells but should be withdrawn to permit a residual population of sensitives to repopulate the tumor, holding the proliferation of the resistant cancer cells in check through lack of resources.

In responding to therapy resistance, drug development seeks synergies and combination therapies that offer different modes of action and place different demands on the cancer cells. In-line with pesticides and pest management, resistance to a monotherapy is relatively easy but acquiring simultaneous resistance to multiple threats may be exponentially harder or impossible. Yet, resistance does evolve even in response to multiple drugs. A more nuanced approach to drug synergies may be to exploit the rapid evolution of the cancer cells. Double-bind therapies are possible when resistance to one drug inadvertently increases the efficacy of another (92–94). In ecology and evolutionary game theory this is known as predator facilitation when a prey's response to one predator species makes it easier to catch by another. Owls drive desert rodents to hide under shrubs where snakes wait in ambush (95). In exploiting the ability of the cancer cells to evolve quickly to new stressors, one should not give the drugs simultaneously but rather alternate them in a strategic fashion. The paradigm of sequential chemotherapies has been applied successfully in rapidly proliferating hematologic malignancies (leukemias and lymphomas) but the right combination of drugs and timing remains elusive in solid tumors (96).

Extinction therapy is predicated upon the observation that we possess many drugs that can initially cause striking reductions in tumor burden, but the reduction is not durable. Resistance will evolve and this evolution may happen swiftly (97). The current practice of waiting until progression to substantially alter therapy may be evolutionarily unwise. If cancer cells have traits permitting them to respond to novel threats, then the evolutionary event rendering a drug or combination of drugs ineffective likely happened long before progression is evident, it likely occurred shortly before or shortly after remission. Extinction therapy advocates using first and second strikes to first drive the tumor burden down to some nadir (preferably where it appears clinical undetectable), and then immediately following with second strike drugs to prevent evolutionary rescue and to exploit the ecological vulnerabilities of fragmented, damaged, and disconnected small remnant populations of cancer cells. Second strikes may drive such populations below their minimum viable population sizes at which point they cannot recover (97). Bone marrow transplants, for example, destroy the habitat, indeed the entire ecosystem, of leukemia cells, creating a cataclysmic extinction event: a cancer cure (49). In light of cancer cell's evolvability, we may be waiting too long before administering second- and third-line therapies. To the best of our knowledge, this approach has never before been proactively advocated because the evolutionary reasons for its plausibility have not previously been appreciated. The diverse array of existing drugs, and cancer cell's evolvability invites us to use a kick-'em-when-they're-down approach, rather than holding back until there are the ecological indicators (=progression) of therapy failure.

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Conclusion

In conclusion, we should treat the evolution of evolvability as a key property for most patients' cancers, strong convergent evolution. The actual traits in cancer cells that generate heritable variation to fuel natural selection may be quite varied, deserve detailed study, and should be clinically measurable. The traits that confer evolvability likely explain the near certainty of both metastasis and therapy resistance; and explain the positive association between a cancer's capacity for metastasis and its capacity for therapy resistance. Knowing that these are linked processes invites therapies that target this capacity to evolve where both drug efficacy can be extended, and metastases prevented—a double win. Furthermore, understanding that cancer cells can swiftly evolve responses to novel and varied stressors create opportunities for adaptive therapy, double-bind therapies, and extinction therapies; all involving strategic decision making that steers and anticipates the coevolutionary responses of the cancers (98).

Disclosure of Potential Conflicts of Interest

K.J. Pienta is a consultant at CUE Biopharma, Inc. No potential conflicts of interest were disclosed by the other authors.

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