

Learning Objectives for Weaving Evolutionary Thinking into Medical Education

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Abstract Basic science is integral to medical education because it teaches future physicians the fundamental principles of biology they need to become lifelong learners and keep up with expanding medical knowledge. One of these fundamental principles is evolution, which has many practical applications in medicine. Consequently, there is increasing interest in integrating evolutionary biology into medical education. To realize this goal, educators should focus on practical aspects of how knowledge of evolution improves a physician's ability to prevent, diagnose, and treat disease. This perspective should be woven throughout the curriculum, so evolution comes to be seen as a broadly relevant concept rather than a distinct and peripheral discipline. In particular, we suggest that three general learning objectives be integrated broadly into medical education. First, medical students should be able to apply knowledge of human evolutionary history to explain how genetic variation within and among human populations affects risk, diagnosis, and treatment of disease. Second,

students should understand how evolution has led to variation within and between pathogen populations (and tumors), affecting diagnosis and treatment. Third, students should understand how analytical tools from evolutionary genetics are used to determine patient ancestry, disease risk, and pathogen origins. We provide multiple specific topics, case studies, and learning activities within each of these three objectives. The evolutionary medicine learning objectives listed here meet multiple competencies and objectives outlined in the Association of American Medical Colleges (AAMC)/Howard Hughes Medical Institute (HHMI) 2009 report on the *Scientific Foundations for Future Physicians*.

Keywords Coevolution · Evolutionary biology · Genetic drift · Natural selection · Race

Why Integrate Evolutionary Biology into Medical Education?

Evolutionary biology and medicine have long been viewed as separate, disconnected disciplines. The study of evolution is often associated with abstract questions concerning the historical origins of current-day biological phenomena, with limited focus on practical applications. Medical school curricula have therefore devoted little attention to evolution. However, evolutionary biology does provide vital conceptual tools that improve learning and practice of medicine. Consequently, the past two decades have seen a proliferation of evolutionary medicine textbooks [1–6] and review articles [7–14].

Nevertheless, few medical schools have effectively incorporated evolution into their curriculum. This continued resistance to evolutionary medicine comes from several sources. The first and major barrier is that medical curricula are

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already overburdened by the fast-expanding body of relevant biomedical knowledge. Medical knowledge is simply too large to convey in a 4-year curriculum, and adding a new topic (evolutionary medicine) will inevitably meet resistance. However, the growing body of biomedical knowledge makes it ever more important that medical education give students the intellectual tools they need to be lifelong learners. We argue that evolutionary biology's integrative view of biology helps students assimilate and understand new biological information. Just as organic chemistry is an essential tool to allow medical students to understand key principles, a foundation in evolutionary biology helps students contextualize new information about anatomy, genetics, physiology, microbiology, or immunology, aiding understanding and memory.

A second source of resistance is a widespread assumption that students have already learned evolution, so it does not need to be covered in medical school. But, an advanced undergraduate evolution class is not required for admission to any US medical school [15], nor is it a required part of many undergraduate biology curricula. In a nationwide survey of 403 biology programs in the USA, less than 20% of programs required an advanced evolution class, and only 70% even offered such a class [16]. Thus, many medical students may not have studied evolution since a brief exposure in an introductory undergraduate biology class. Nor can we assume that US medical students learned evolution in secondary school, where a third of teachers promote creationist concepts and many more avoid the topic entirely [17]. As a result, many medical students harbor fundamental misconceptions about how evolution works and its implications [18]. These misconceptions will persist unless specifically addressed within the context of their medical education.

Third, many evolution courses focus on broad conceptual principles and do not directly address the relevance of evolution to medical practice. Even students (or, instructors) who understand evolution well may not know how it applies to their chosen career. The growing field of evolutionary medicine does not always help in this regard, when it focuses on explaining the historical origins of disease (e.g., “Why does menopause occur?”, “Why do we experience lower back pain?”) as opposed to guiding physicians' decision-making. The historical origins of human traits can be intellectually fulfilling and might even facilitate student learning but does not necessarily change daily medical practice. Educators with limited classroom time are thus likely to omit such topics.

However, evolutionary biology provides more than just an intellectual framework to explain the origins of human conditions. We suggest that there are three very general reasons why evolution is relevant to the daily *practice* of medicine:

1. Understanding the evolutionary origins of genetic diversity within and among human populations helps physicians make appropriate diagnoses and plan treatments.
2. Pathogens and tumors are evolving populations. We must account for their evolution during diagnosis, treatment, and control
3. Evolution provides analytical tools, such as phylogenetics and population genetics, that are used in diagnostics to identify pathogens, trace sources of infection, determine patient ancestry, and interpret genetic markers of disease risk.

We suggest that teaching these ideas in medical school will improve medical practice in three ways. First, *understanding evolution can improve diagnosis*. For example, familiarity with human evolutionary history and genetic diversity can help physicians avoid racial stereotyping that can lead to misdiagnosis of genetic disorders (case study in box 1). Second, *understanding evolution can improve preventative or treatment plans*. For example, physicians should have an accurate understanding of natural selection when treating pathogens or tumors that may evolve resistance to drugs (case study in box 2). Third, *evolution provides an integrated conceptual framework that helps students learn medical concepts*, particularly via comparative anatomy and physiology, and understanding the genetic, environmental, and pathogenic causes of disease.

In recognition of these benefits, the Association of American Medical Colleges (AAMC) and Howard Hughes Medical Institute (HHMI) specifically called for greater inclusion of evolution in medical training in their report, “*Scientific foundations for future physicians*” [19]. The report asserted that “integration of clinical education and basic science often lacks sufficient emphasis on fundamental scientific principles that are key to lifelong learning and biomedical scientific literacy. Understanding these principles is essential to empower physicians to continue to comprehend their own disciplinary literature and to evaluate critically claims of therapeutic effectiveness...”. Consequently, the AAMC/HHMI report specifically lists evolutionary concepts within various competencies. The goal of this paper is to elaborate on those competencies and make specific suggestions for how evolutionary biology can be integrated into medical education to meet the AAMC/HHMI recommendations. We do so by identifying broad learning objectives, within which we list specific learning objectives and competencies, supported by case studies and activities to teach and achieve those objectives. Our specific learning objectives and case studies are summarized in Supplementary Appendix Table 1, indexed to relevant AAMC/HHMI competencies.

Evolution as a Thread Woven Throughout Medical Training

The first US medical schools to incorporate evolutionary medicine have typically done so by offering an elective class on

the subject. Courses in evolutionary medicine are available or pending at medical schools at a number of institutions including Yale University, the University of California at Los Angeles, Arizona State University, and the University of Texas at Austin. However, the practice of offering evolutionary medicine as a distinct class, particularly as an elective, reinforces the misconception that this is an optional topic separate from mainstream medical practice (note, this is not intended as a criticism of these courses, which needed to gain a foothold within a packed curriculum). Instead, we reiterate the oft-stated point that evolution is a recurrent organizing theme of biology that has applications in many contexts throughout basic biological training and medical practice. Accordingly, evolution should be seamlessly woven throughout the medical curriculum at frequent intervals within each of many topics (e.g., anatomy, genetic disorders, microbiology, immunology, population health). We therefore advocate that medical educators promoting evolutionary medicine work with a broad swath of instructors throughout the curriculum to identify topics relevant to each of many subjects. To facilitate this integration, we present a set of learning objectives and illustrative case studies here that span many areas already within typical medical curricula. These case studies are common to most medical school curricula and highlight the ease with which an evolutionary medicine thread can be incorporated into established programs. We envision the inclusion of evolutionary medicine learning objectives in short

discussions, lecture modules, or exercises. Furthermore, considering the value of evolutionary thinking in patient diagnosis and treatment, we encourage the application of these concepts in case-based and problem-based learning activities.

Learning Objectives in Applied Evolutionary Medicine

Below, we outline three *general learning objectives* concerning evolutionary medicine (Fig. 1). In developing these learning objectives, we emphasized the application of evolution to medical decision-making related to prevention, diagnosis, and/or treatment. We do note, in places, where evolution can provide an intellectual scaffold to facilitate learning medical topics (e.g., evolutionary comparative anatomy may aid students in learning about human anatomy), but that is not our focus.

Within each of these, we present multiple *specific learning objectives*. Each specific learning objective is described in greater detail in the online Supplemental Materials (S.M.), where we describe multiple relevant case studies, cite relevant sources, and suggest activities and exercises. We cannot, in the interest of space, provide an exhaustive list of relevant cases, but we provide an extended online S.M. section that elaborates on the ideas introduced below and provides more case studies. The learning objectives we propose are cross-

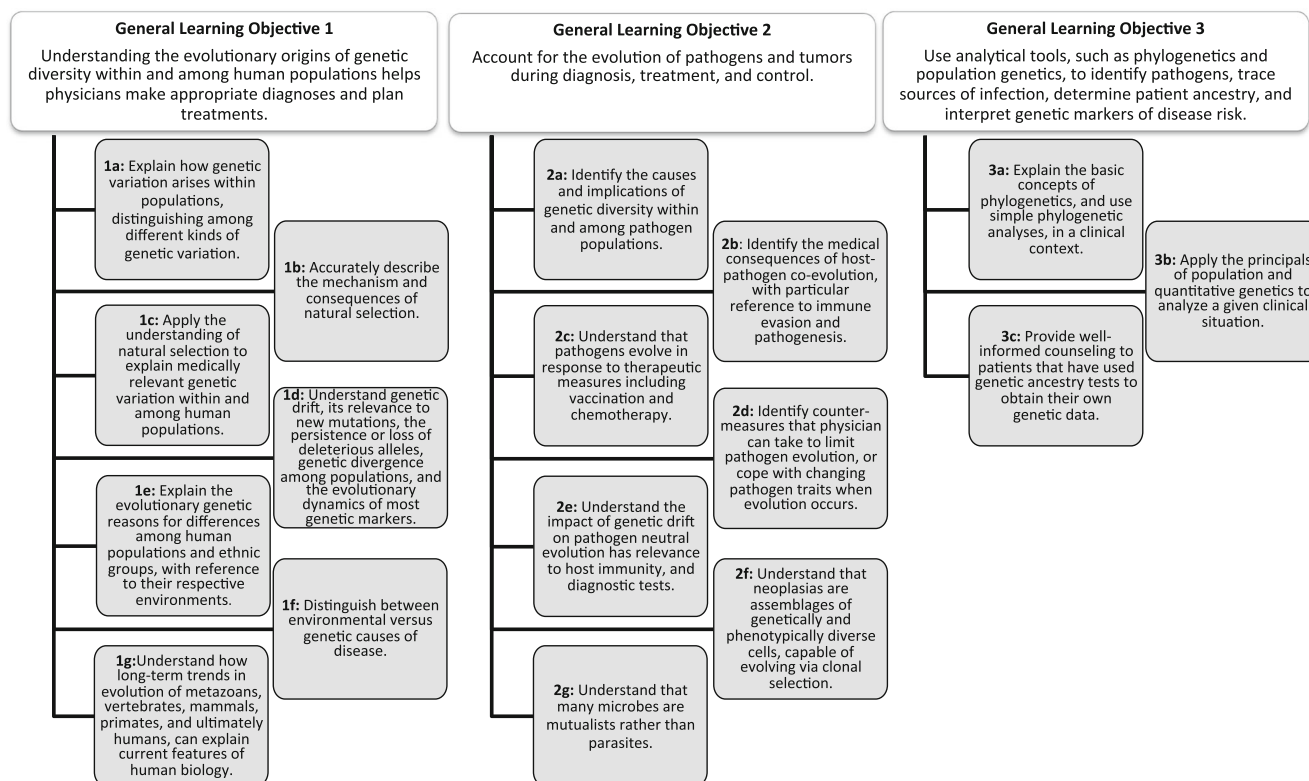


Fig. 1 An overview of our recommendation for learning objectives for evolutionary medicine

referenced in the S.M. to competencies and objectives in the AAMC/HHMI 2009 report. Notably, some of the objectives listed below are in fact already part of many medical curricula, albeit not explicitly acknowledging that they are evolutionary concepts.

General Learning Objective 1

Physicians should be able to explain how past and contemporary human evolution has led to genetic variation within and among human populations and how this variation affects decisions regarding disease prevention, diagnosis, and/or treatment.

Specific Learning Objective 1a: Students should be able to explain how genetic variation arises within populations, distinguishing among different kinds of genetic variation. This competency illustrates students' understanding of the spectrum of mutational processes including point mutations, insertion/deletions, repetitive sequences [20, 21], mobile genetic elements [22, 23], selfish genomic parasites [21], copy number variation [24–26], chromosomal duplications or rearrangements [25, 27, 28], uniparentally inherited variants (e.g., mitochondrial diseases; [29–31]), and heritable epigenetic modification of the genome [32]. Students should be able to identify (i) genetic disorders arising from each type of genetic variant, (ii) how the variant causes disease, (iii) genetic tests for disease risk, and (iv) prevention or treatment options. In addition to these comparatively simple single-gene disorders, it is essential that students learn about complex polygenic diseases that entail many possible mutations at many different genes [33]. They should be able to distinguish between spontaneous de novo mutations (e.g., from non-homologous recombination during gametogenesis) versus standing genetic variation within populations. Related specific objectives, described in the S.M., address the geographic origins of mutations and consequent variation in disease risk among human populations. The next specific learning objectives address why such mutations persist within populations.

Specific Learning Objective 1b: Students should be able to accurately describe the mechanism and consequences of natural selection. A correct understanding of this subject is a prerequisite for many subsequent learning objectives in evolutionary medicine, as well as key topics in microbiology and immunology. Addressing this topic early on in a curriculum allows an instructor to identify and correct misconceptions common to biology majors graduating from university. In the S.M., we elaborate on several common misconceptions about selection, as they apply to human health, illustrated with specific biomedically relevant case studies.

Specific Learning Objective 1c: Students should be able to apply their understanding of natural selection to explain medically relevant genetic variation within and among human

populations. Students should know how the history of natural selection can help identify patients at risk for genetic disorders based on their ancestry, geography, and ethnicity.

Specific Learning Objective 1d: Students should understand the process of genetic drift and its relevance to the fate of new mutations [34, 35], the persistence or loss of deleterious alleles, the genetic divergence among populations, and the evolutionary dynamics of most genetic markers. Understanding the role of random processes in evolution helps physicians appreciate that not all genetic variants and human traits are adaptive and provides essential background to understand the logic of ancestry testing and association mapping. Importantly, when students engage with the details of recent human evolution, they can develop a sophisticated understanding of the distribution of genetic variation that transcends overly simplistic racial categories (see S.M. for examples).

Specific Learning Objective 1e: Students should be able to explain the evolutionary genetic reasons for differences among human populations and ethnic groups, with reference to their respective environments. Students should be able to integrate principles of population genetics (natural selection, genetic drift, migration) to accurately explain patterns of human genetic variation among populations [36] and apply this knowledge to evaluate patients' disease risk using genetic ancestry data.

Specific Learning Objective 1f: It is essential that physicians learn to distinguish between environmental versus genetic causes of disease. The former can often be treated by environmental modification, while the latter cannot. The distinction between genetics and environment is often blurred during discussions of ethnicity, race, and racial health disparities in medical classrooms and in biomedical research more generally [37–40]. Thus, a clear understanding of evolutionary genetics can help physicians evaluate the relative roles (or, interaction) of genetics and environment in disease and implications for diagnosis and treatment.

Physicians should be able to clearly identify diseases with substantial environmental contributions. This includes the effects of social conditions and environment on risk of exposure to toxins or pathogens, to identify patients that are at high risk and identify strategies to minimize that risk. Evolutionary genetics (particularly quantitative genetics) provides a formal framework for measuring and identifying such environmental effects on individuals' traits, including "genotype by environment interactions" (when environmental effects differ among genotypes). Training in evolutionary genetics therefore gives physicians a rigorous framework for understanding the complex interplay between individuals' environment and multi-locus genotype in determining disease risk, thereby informing strategies to prevent or treat disease.

Specific Learning Objective 1g: There is one final aspect of human evolutionary history that we view as a valuable component of medical education, but which does not have direct application to medical practice in the form of prevention,

diagnosis, or treatment. We believe that physicians should understand how long-term trends in the evolution of metazoans, vertebrates, mammals, primates, and ultimately humans can explain current features of human biology, ranging from derelict genes to features of embryogenesis, anatomy, and physiology [41]. We posit that a working knowledge of comparative anatomy or physiology, and evolutionary history, provides a logical context to understand how features of human biology arose. Furthermore, evolutionary comparative anatomy provides a conceptual framework that we predict will appreciably aid medical students in learning and retaining basic details of human anatomy or function. We do not advocate implementing this objective blindly, as at present, it is merely our supposition. We require well-controlled studies that test our suggestion that an evolutionary scaffold can in fact improve medical student learning.

General Learning Objective 2:

Physicians should be able to explain the medical significance of evolution in disease-causing agents including microorganisms, protists, helminths, and neoplasias. Medical students should be able to identify therapeutic strategies that minimize or compensate for pathogen evasion of host immunity, vaccines, or drugs. The following specific learning objectives elaborate on these ideas, again with details and suggested case studies relegated to the S.M.

Specific Learning Objective 2a: Students should be able to identify the causes and implications of genetic diversity within and among pathogen populations, including mutation, recombination, horizontal gene transfer, etc. This objective is to train physicians to view pathogens not as invariant entities but as diverse and changing populations, whose treatment must be modified accordingly.

Specific Learning Objective 2b: Physicians should be able to identify the medical consequences of host-pathogen coevolution, with particular reference to immune evasion and pathogenesis. This provides a conceptual grounding for understanding why many pathogens alter their surface antigens, establish infections in immune-privileged host tissues, actively manipulate host immune function, and/or exploit host immune cells [42–46]. This immune escape explains, for example, many helminths' ability to establish long-lived infection in immunologically active host tissues.

Specific Learning Objective 2c: Pathogens evolve not just in response to host defenses (objective 2b) but also in response to therapeutic measures including vaccination and chemotherapy. A particularly dramatic visual example of evolutionary escape from antibiotics was recently provided by a new study [47]. Physicians must clearly understand the role of evolution in the spread of therapy resistance (most notably, antibiotic resistance [48–56]) and how evolutionary principles can guide more

appropriate use of therapies. Physicians should be prepared to explain these concepts to patients, for example (i) to induce them to complete full courses of antibiotics, (ii) to understand why antibiotics should not be over-used, or (iii) to understand why some vaccines must be renewed regularly (e.g., influenza).

Specific Learning Objective 2d: Physicians should know countermeasures that reduce the risk of pathogen evolution or cope with changing pathogen traits when evolution occurs. Physicians should anticipate that resistance is likely to evolve and can do so within a single patient [57]. Physicians should know how to identify this within-patient evolution and know when it is most likely to happen (e.g., in patients with compromised immune systems or those battling novel pathogens, e.g., H5N1).

Specific Learning Objective 2e: Genetic drift is also applicable to pathogens, and the resulting neutral evolution has relevance to host immunity and diagnostic tests. Drift can be especially strong in pathogens because they often go through large bottlenecks during transmission among hosts. This can lead to the accumulation of deleterious mutations within some pathogen lineages or may drive evolution of new pathological effects (e.g., pandemic influenza [58]). The bottlenecks also mean that different hosts may be infected with different genetic variants, and different amounts of genetic diversity, leading to patient-specific potential for within-host evolution.

Specific Learning Objective 2f: Neoplasias are assemblages of genetically and phenotypically diverse cells that are capable of evolving through time and during metastasis via clonal selection ([59] see S.M. for details). Physicians should understand the role of natural selection in cancer origination, identification, progression, metastasis, and treatment. Treatment plans must keep this evolutionary potential in mind, both to mitigate the potential for evolutionary escape from chemotherapy and to improve treatment and prognosis by tailoring plans to the particular cancer lineages currently extant within a patient.

Specific Learning Objective 2g: In recent years, there has been fast-growing interest in the observation that many microbes are mutualists rather than parasites. Beneficial symbionts (including macroparasites, bacteria, viruses, and fungi) have coevolved mutually helpful relationships with humans and other vertebrates, often involving highly regulated molecular interactions between the host and microbes [60]. Physicians should understand that past coevolution has led to this beneficial interaction which, when perturbed (dysbiosis), can lead to a variety of disease states. Physicians should be able to distinguish between a healthy and unhealthy microbiota (a fast-changing area of research) and understand the mechanisms by which these microbes can undermine or improve human health. This includes the role of the normal microbiota in the development, immunity, nutrition, and homeostasis, including mechanisms of immune tolerance [60–75].

General Learning Objective 3:

Medical informatics is transforming medical practice in many respects. Evolutionary biology has contributed a variety of bioinformatic tools that are applied in biomedical research and, increasingly, in medical practice. In particular, the evolutionary fields of phylogenetics, population genetics, and quantitative genetics have seen fast-expanding applications in medicine. Students should understand how these tools work and can be used by physicians to make decisions concerning diagnosis or treatment.

Specific Learning Objective 3a: Students should be able to correctly explain the basic concepts of phylogenetics and use simple phylogenetic analyses, in a clinical context. Examples of phylogenetic applications include the phylogenetic identification of unknown symbionts (e.g., metagenomic analysis of gut microbes [76, 77]) or pathogens [78–80] using phylogenetic comparative analyses of DNA sequences.

Specific Learning Objective 3b: Population and quantitative genetics are evolutionary subdisciplines designed to study changes in genotypes and phenotypes through time or across a landscape. In a biomedical context, these disciplines have yielded analytical tools for studying infectious disease evolution including the evolution of virulence and drug resistance. For instance, drug treatments of HIV patients have been shown to induce rapid evolution of the virus within single patients [81]. Monitoring sequence evolution in a patient's viral population can therefore alert a physician to viral escape, before new symptoms arise, and can guide subsequent treatment decisions [82]. Physicians who are aware of these tools will be able to apply them to identify rare diseases or anticipate a pathogen's evolutionary escape.

Specific Learning Objective 3c: Genetic ancestry tests are widely used by individual patients, both to obtain genealogical insights and to detect disease risks. Direct-to-consumer genetic testing is built on statistical analyses that rely on human evolutionary history. Future physicians will have to provide well-informed counseling to patients who have obtained their own genetic data. As with all the above learning objectives, we elaborate on these ideas in the S.M.

Conclusions

Many of the recommendations listed above touch on topics already covered in medical education (e.g., the evolution of antibiotic resistance, issues pertaining to ancestry, genetic variation in disease risk). These are not just disparate topics, however. They share a common theme: Past and ongoing evolution has generated genetic variation within and among populations of humans, pathogens, immune cells, and even within tumors in individual patients. This genetic variation can mean that a one-size-fits-all strategy may not be effective

at treating a disease. Instead, physicians may need to adopt new approaches to disease prevention, diagnosis, or treatment. This response may be tailored to the particular genotypes of the patient or disease, or the new response might represent a pre-emptive strategy to inhibit disease evolution. In essence, evolutionary biology is the *raison d'être* of personalized medicine. But the application of evolutionary ideas goes far beyond this emerging medical concept. Evolution affects how drugs are designed, what drugs we administer, and when and to whom they are prescribed. Understanding evolution can alter physician's perceptions of race and ethnicity, thereby changing and improving how they interact with patients.

Perhaps most importantly, but less concretely, evolution gives a scientific explanation for why humans and pathogens function as they do. We propose that this explanatory framework should help medical students learn material by organizing facts into a broader context and can help physicians assimilate new biomedical findings throughout their career after medical school. To date, studies directly examining the impact of an evolutionary framework on student learning and clinical skills have not yet been performed. We propose that such studies would provide valuable insight into curriculum design in undergraduate medical education. In short, we suggest that evolution represents a key biological concept that should be integrated, where relevant, throughout a medical curriculum. Not because we wish physicians to appreciate the intellectual elegance of the idea, nor because they need to know about peppered moths, or Galapagos finches, or the Cambrian explosion, but because evolution helps doctors learn biology and apply that knowledge correctly when treating their patients.

Box 1: Teaching Human Evolution to Avoid Racial Stereotyping

Cystic fibrosis is a disease of the secretory glands caused by the dysfunction of the CFTR gene, which codes for chloride ion channels in epithelial cell membranes. The disease is much more common in people with European ancestry (1 in 3300) compared to those with African and Asian ancestry (1 in 15,300 and 1 in 32,100, respectively) [83]. Cystic fibrosis causes the buildup of thick, sticky mucous in the airways, which results in frequent attacks of bronchitis and pneumonia in the early stages of the disease. More than 71% of cystic fibrosis cases are diagnosed before the age of 1 [83]. Because the symptoms of CF are relatively common, physicians sometimes miss the diagnosis of cystic fibrosis in an individual who they classify as non-white if they mistakenly believe that CF occurs only in white patients. For example, in California, a 2-year-old black female patient was described by her doctors as presenting a fever and cough. Two years later, this same girl presented with "another pneumonia." However, her physicians never considered the possibility of cystic fibrosis due

to her race. This patient only received the proper diagnosis at the age of 8 when a passing radiologist, with no knowledge of the case, saw her chest X-ray and asked about the “CF case” [84]. The initial physicians had not appreciated the role of gene flow among populations and the consequent presence of CF in non-European populations. If these physicians had had a better understanding of the tenuous relationship between population genetics and race, the patient may have been diagnosed and treated earlier. At present, there are few formal analyses of the extent to which racial stereotyping leads to misdiagnosis. However, it is clear that racial profiling is currently common in medicine and can affect physicians’ diagnostic and treatment decisions [85–87].

Box 2

Cancer treatment is an area of clinical medicine that stands to gain the most from an increased understanding and application of evolutionary theory. Tumors are heterogeneous populations of cells that evolve over time and adapt to environmental stressors such as the introduction of drug therapy. This knowledge can lead to novel therapies, as in the case of glioblastoma, an aggressive form of brain cancer. Chromosomal amplifications of epidermal growth factor receptor gene (EGFR) are characteristic of glioblastoma. Tumor cell populations that possess both chromosomal amplifications of EGFR and a rare mutation of the gene (EGFRvIII/DEGFR) are correlated with increased tumor cell proliferation [88]. A 2010 study by Inda et al. found that a small group of tumor cells possessing these variants greatly increases the growth of the tumor as a whole, through the activation of IL-6 and LIF cytokines which activate the expression of EGFR in neighboring cells through gp130, a subunit of the IL-6 receptor. These researchers demonstrated that tumor growth could be stopped by interfering with IL-6, LIF, or gp130 [89]. Understanding a tumor as a variable population of cells and applying the tools of molecular and evolutionary genetics could lead to better patient outcomes.

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