He revolution in genomics is transforming medicine.¹ Among its important contributions is a demonstration — through a greater understanding of the human genome and the microbiome — that evolutionary biology underpins the principles and practice of medicine. Evolutionary medicine provides the unifying framework by which clinical and public health physicians can incorporate genomics into medicine. It reconsiders the questions, “what is a patient?” and “what is a disease?” Some areas of medicine have already incorporated genomics and evolutionary medicine into clinical practice (e.g., the disciplines of genetics, infectious diseases and cancer care). Other areas of medicine are likely to follow as new research emerges, and the practice of medicine will be increasingly based on an evolutionary understanding of the human genome and microbiome.

What is evolutionary medicine’s view of disease?

The World Health Organization (WHO) lists about 12,000 diseases in its International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). More than 6000 drugs are used in treatment, along with 2500 surgeries and 1500 other medical interventions.² For evolutionary medicine, the causes of disease are more simply conceived.³ At the general level, diseases can result from extrinsic or intrinsic causes. At a finer level, six categories of disease are conceptualized that capture both evolutionary and mechanistic causes (Table 1), which will be discussed in more detail later.

How does evolutionary medicine view the patient?

Evolutionary medicine views patients as individuals whose history has unfolded over the course of an entire life cycle,⁴ beginning at fertilization and progressing through birth, growth, maturation and aging. Human life histories are remarkably uniform, but with unique windows of vulnerability during which the environment affects genome expression. In particular, fetal phase, infancy and childhood are uniquely vulnerable to environmental forces as shown in a review of studies on the developmental origin of disease.⁵ The remarkable expansion of the human lifespan occurring during the past century, which followed a dramatic reduction in childhood mortality, is an example of a trait that shows the plasticity of life history.⁶ Epigenomic studies may show the biochemistry that underpins the plasticity of lifespan and its responsiveness to early life events, which may have great potential for development of new treatments for chronic diseases.

Like all organisms, humans age. From an evolutionary perspective, aging exists because the chances of reproducing progressively decrease over time owing to the accumulated risk of death from extrinsic causes. Thus, there is stronger natural selection to maintain health at younger ages than at older ages, and this selection can favour genes that are beneficial in youth but detrimental in old age. Such genes produce antagonistic pleiotropy and tend to accumulate in the genome through evolutionary time.⁷ Many diseases of aging are thought to be due to the effects of antagonistic pleiotropic genes on intrinsic homeostatic and maintenance processes. The gene for interleukin-6 (IL-6) may be an example of antagonistic pleiotropy. Interleukin-6 is tightly regulated in early life but dysregulated in late life, and elevated levels of IL-6 are associated with several age-related chronic inflammatory diseases.⁸ Genomic and epigenomic studies of patterns of mortality among older adults should uncover those genes that display antagonistic pleiotropy.

KEY POINTS

- The practice of medicine will increasingly be based on an evolutionary understanding of the human genome and microbiome.
- According to the evolutionary medicine framework, disease is conceptualized within six categories that capture genetic, evolutionary and mechanistic causes.
- Evolutionary medicine views patients as individuals whose history has unfolded over the course of an entire life cycle with unique windows of vulnerability during which the environment affects genome expression; the microbiome has co-evolved with animal hosts and protected the host against pathogens, assisted in digestion of food and in the development of the immune system.
- Although evolutionary medicine requires further research to develop its distinctive viewpoint, it offers a secure foundation for future developments in medicine.
How has the human genome evolved, and what are the implications for medicine?

A genome necessarily includes all protein-coding genes together with other functional and nonfunctional DNA elements that interact as an integrated entity that is vertically transmitted between generations. Although genes encode proteins, genomes encode organisms. Because segments of an individual genome are randomized at meiosis during gamete formation, genomes are assembled anew with each generation. Thus, it is genes and not genomes that are stable enough for natural selection to act on over evolutionary time scales. The evolutionary age of human genes varies considerably. About 20% are universal ancient genes with a subset of about 70 genes common to all cellular life on earth. Most of these genes are related to protein synthesis. About 40% of human genes are shared among all eukaryotes, which include metabolic and other genes essential to cellular function. Some genes have been shaped by billions of selection events and are finely tuned without variation in the human genome. Such genes are fixed parts of the genome and include metabolic genes, which had their origin between 1.6 and 3.9 billion years ago. Genes for other parts of the human body have a much more recent evolutionary origin and, correspondingly, have been shaped by far fewer selection events. These include genes for hairlessness, dark skin colour and abundant sweat glands, which originated during the last 2 million years of evolution within the genus Homo. Much genetic, phenotypic and fitness variation exists among these younger genes in the human genome.

Comparisons between genomes of chimpanzees and humans suggest that the origin of the genus Homo was characterized by the head-to-head fusion of two ancestral chromosomes to form human chromosome two, resulting in the reproductive isolation of descendents within the genus Homo. Phenotypic traits that evolved within the Homo lineage include delayed maturation, menopause and longevity, as well as changes in postnatal brain development resulting in the evolution of childhood with learning by imitation, descent of the larynx for the development of rich spoken language, reshaping of an opposable thumb for tool manipulation and enhanced T- and B-cell function, possibly enabling humans to live in higher-density social groups. Genome analysis is beginning to uncover the genetic basis for these distinctive Homo phenotypes.

What is the role of the evolving microbiome?

Genomics has also elucidated the remarkable microbiome that coats all human mucosal surfaces with at least as many microbial cells as the number of somatic cells that compose the human body. The most varied microbiome is found in the gastrointestinal tract. The microbiome has co-evolved with animal hosts and protected the host against pathogens, and assisted in digestion of food and in the development of the immune system, which in turn enabled the growth of the body to large size during vertebrate evolution.

Originally, the physiologic function of the immune system may have been the management of the commensal microbiome. The immune system is based on molecular recognition of commensal and pathogenic microbes. Discriminating between the molecules of pathogens and the molecules of the microbiome selected for the development of the adaptive immune system occurred around 500 million years ago. The older innate immune system that recognizes conserved microbial molecules is controlled by genes that also regulate the relation between host and microbiome. Through mutations, these genes may produce proteins that cause a spectrum of inflammatory diseases such as ulcerative colitis and Crohn disease. The gastrointestinal microbiome at the phyla level is remarkably similar from human to human. However, at the species and strain level each microbiome is nearly unique to an individual. The diversity and metabolic phenotype of the microbiome changes over the human life cycle. In addition, characteristic changes in the microbiome have been correlated with a variety of diseases. There is speculation that different microbiomes produce different disease phenotypes. A genome necessarily includes all protein-coding genes together with other functional and nonfunctional DNA elements that interact as an integrated entity that is vertically transmitted between generations. Although genes encode proteins, genomes encode organisms. Because segments of an individual genome are randomized at meiosis during gamete formation, genomes are assembled anew with each generation. Thus, it is genes and not genomes that are stable enough for natural selection to act on over evolutionary time scales. The evolutionary age of human genes varies considerably. About 20% are universal ancient genes with a subset of about 70 genes common to all cellular life on earth. Most of these genes are related to protein synthesis. About 40% of human genes are shared among all eukaryotes, which include metabolic and other genes essential to cellular function.

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### Table 1: Disease categories in evolutionary medicine

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrinsic cause</td>
<td>Infectious diseases, trauma, starvation, malnutrition and toxins</td>
</tr>
<tr>
<td>Intrinsic cause</td>
<td></td>
</tr>
<tr>
<td>Diseases that are adverse effects of host defenses</td>
<td>Autoimmune diseases, asthma and allergies</td>
</tr>
<tr>
<td>Diseases of disordered homeostasis</td>
<td>Type 2 diabetes mellitus, atherosclerosis and hypertension</td>
</tr>
<tr>
<td>Diseases resulting from age-related loss of maintenance</td>
<td>Neurodegeneration, sarcopenia, reduced renal function, osteoporosis and cancer</td>
</tr>
<tr>
<td>Genetic, genomic and chromosomal diseases</td>
<td>Mendelian diseases, trisomies and Turner syndrome</td>
</tr>
<tr>
<td>Maternal, paternal and fetal genetic conflict disorders</td>
<td>Eclampsia, gestational diabetes and possibly schizophrenia and autism</td>
</tr>
</tbody>
</table>
different dominant metabolites, which, by methylating DNA or acetylating histones, epigenetically alter gene expression and thereby affect metabolism or immunity.\textsuperscript{25}

What are the categories of disease causation according to evolutionary medicine?

Table 1 summarizes the six categories of disease causation according to evolutionary medicine. As medical, public health and societal efforts have reduced the burden of extrinsic causes of disease, diseases of intrinsic origin have become increasingly common. Intrinsic diseases result from imperfections in the evolution of genome owing to constraints, trade-offs, antagonistic pleiotropy and changes to the environment that occur faster than the genome is able to adapt.

**Category 1: Diseases with extrinsic causes**

Extrinsic causes of disease include infection, altered microbiomes, starvation and malnutrition, injuries, hypoxia, hypo- and hyperthermia, and exposure to noxious xenobiotics among others. Infectious diseases are a primary cause of category 1 diseases and offer one of the most striking examples of the impact of genomics on medicine.\textsuperscript{26} Evolutionary medicine previously uncovered the important concept of microbial trade-off between modes of transmission and evolution of virulence,\textsuperscript{27,28} and genomics showed how pathogens evolved virulence traits as they adopted horizontal modes of transmission. For example, extensive phylogenomic analysis of the pathogenic bacterial phylum Chlamydiae resolved its ancient evolutionary origins, core complement of genes, niche and tissue-specific genomic adaptations, evolved virulence mechanisms and those proteins that preferentially interact with the T-cell immune system.\textsuperscript{29–32}

Genomics has also been used for tracing the evolutionary history of pathogens as they transmit within populations. A recent example illustrates the power of genome evolution to elucidate the origin and transmission of a tuberculosis (TB) outbreak.\textsuperscript{23} An outbreak of 41 cases of TB occurred in a medium-sized community in British Columbia over a three-year period. The outbreak was investigated epidemiologically and genomically. Figure 1A provides the epidemic curve. Initially, the outbreak appeared to be due to a single strain of TB, and it was

![Figure 1](image-url)
unclear whether a “virulence” mutation in the TB genome or changes in social conditions of the community had occurred. Genomic analysis of the mutation patterns of TB isolates as they replicated within their individual hosts was used to discover the transmission pathway between hosts. This analysis showed that the outbreak was caused by two distinct lineages of *Mycobacterium tuberculosis* that existed in the community before the outbreak. Genomic analysis clearly showed the central importance of just three individuals in the transmission network (Figure 1B). Epidemiologic investigation of these individuals showed that the introduction of crack cocaine into this community likely triggered the outbreak.

**Category 2: Diseases that reflect adverse effects of the body’s defenses**

The defence system of the human body provides a large evolutionary benefit, in particular when the threat of infectious disease is high. However, the benefit diminishes when infectious disease is well-controlled; then the high cost of the defence system becomes apparent. Diseases in this category include autoimmune diseases, allergies and possibly behaviours such as obsessive-compulsive and anxiety disorders. It is notable how rapidly these diseases emerged during the 20th century as diseases in category 1 came under control.

**Category 3: Diseases of disordered homeostasis**

When culture changes much more rapidly than the genome can respond, “mismatch” diseases occur. These may be unique to humans because of the dominance of culture. These include obesity, type 2 diabetes, atherosclerosis, hypertension and addictive behaviours. Although the epigenomic and gene–environment basis for mismatch diseases are yet to be fully uncovered, it seems that they occur when normal physiologic systems that have adjustable set points are locked into a pathologic state.

**Category 4: Diseases resulting from age-related loss of maintenance mechanisms**

Age-related limitations in organ, tissue, and cellular repair, unregulated inflammation, impaired autophagy, failure to eliminate misfolded protein, and loss of fidelity in genome repair are most likely due to the pathophysiological effects of genes that display antagonistic pleiotropy. Diseases characterized by neurodegeneration, sarcopenia and reduced renal function, as well as osteoporosis, arthritis, cancer, atherosclerosis and type 2 diabetes are associated with such processes. Relative to other species, humans are at high risk of cancer; evolutionary medicine explains that this occurs because of long postreproductive life in humans where natural selection has been too weak to select for highly efficient mechanisms of cancer prevention against random mutations in the somatic stem cell genome. The gene for p53 encodes for a tumour suppressor protein and is an example that displays antagonistic pleiotropy. p53 protects against cancer up to a level beyond which further increases accelerate death from aging.

**Category 5: Genetic, genomic and chromosomal diseases**

Evolutionary genomics in medicine began with the identification of diseases that are caused by single gene mutation; more than 3600 Mendelian diseases have been identified. No specific defenses have evolved against these diseases, and natural section most often eliminated affected individuals from the population. As human mating with first and second cousins decreases, there seems to be a corresponding decline in the impact of recessive Mendelian diseases. However, many of these diseases recur in populations through repeated germline mutations because of the heterozygote advantage of the carrier state. The genetic bases for Mendelian disorders are being diagnosed increasingly by whole exome sequencing, and genome therapy based on clustered regularly interspaced short palindromic repeats (CRISPR) technology is an emerging therapeutic approach to genes that cause Mendelian disease.

**Category 6: Maternal, paternal and fetal genetic conflict disorders**

Human pregnancy is sustained by a highly invasive placenta, in which fetal tissue directly bathes and regulates maternal tissue, and the fetus shares only 50% of its genome with its mother. Fetal–maternal genetic conflict can occur. These disorders include intrauterine growth retardation, eclampsia and gestational diabetes. In addition, chromosomes of maternal and paternal origin in the fetus may come into conflict, possibly contributing to major mental disorders such as autism and schizophrenia. Both Prader–Willi and Angelman syndromes have nearly identical deletions involving chromosome 15 q11–13. Prader–Willi syndrome has a deletion in paternal chromosome 15 and carries a high risk of schizophrenia. Angelman syndrome has a deletion in maternal chromosome 15 and carries a high risk of autism.

**How can evolutionary medicine change our approach to practising medicine?**

The essential advantage of evolutionary medicine is its unifying conceptualization of health and disease. As Theodosius Dobzhansky famously said, “Nothing in biology makes sense except in the light of evolution.” The same appears true of medicine.

The current explanatory framework for medicine is based on mechanism. However, there are at least as many mechanisms as there are genes in the genome. Students of medicine may be daunted by the sheer range of mechanism-based medicine. Evolutionary medicine has the potential to unify the teaching and learning of mechanism-based medicine. Increasingly, there are calls for medical schools to format curricula on an evolutionary medicine basis, although few have done so. By highlighting the importance of evolutionary medicine, the genomic revolution should help to drive this change.

Evolutionary medicine in combination with genomics is being used to guide research that will uncover the importance of the
microbiome, epigenome, gene–environment interaction and antagonistic pleiotropy. Such discoveries may lead to new therapies. A major challenge for funding agencies is how best to take advantage of the evolutionary categories of disease causation in their funding priorities.

Applying evolutionary medicine to clinical practice will not be straightforward. Evolution focuses on genes and clinicians focus on patients. Health is not directly selected by natural selection; rather, it is an indirect effect of organisms selected for reproductive success. Health is the central goal of medicine. Although evolutionary medicine requires further research to develop its distinctive viewpoint, it does provide a secure foundation for future developments in medicine.

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