INFECTIOUS DISEASES

Eradication genomics—lessons for parasite control

Genomic surveillance could help achieve targets for the elimination of tropical diseases

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Large-scale programs are seeking to control or eliminate infectious diseases with the greatest impact on global health. Many of these efforts target the neglected tropical diseases (NTDs) that disproportionately affect the lives of the poor. Often the aim is to eradicate the causative pathogens. The idea—inspired by the success of smallpox eradication in the 1960s and 1970s—is that a large-scale, but time-limited, effort could eliminate a disease for all successive generations, resulting in an enormous payoff both financially and in improved health. Here, we discuss the value of genomic approaches to support disease eradication efforts, particularly by analogy with how conservation genomics is supporting efforts to prevent extinctions.

Although there are fungal, viral, and bacterial NTDs, most are caused by infections with parasites (particularly protozoa and helminths), including the protozoa that cause sleeping sickness, leishmaniasis, and Chagas disease, or worms that cause diseases such as schistosomiasis, hookworm disease, and river blindness. Only two diseases—human smallpox and the cattle disease rinderpest—have been successfully eradicated; both of these campaigns relied on the availability of highly effective and long-lasting vaccines that are not available for any of the parasitic NTDs. Control methods vary between the different diseases and can include controlling parasite carriers (vectors), better sanitation, and improvements to health systems to allow faster detection and treatment. However, the main approach has been large-scale treatment of people at risk of infection, whether they actually have the disease or not. The size of these interventions is astounding: More than 1 billion people were treated for NTDs in 2016, with drugs donated by manufacturers. Nonetheless, this represents only 63% of the treatment needed to fully cover the populations at highest risk (*1*).

Key to the success of NTD control is measuring changes in pathogen populations, to ensure that interventions are on course to achieve elimination goals and to direct additional resources to areas of high or stubborn prevalence. However, monitoring pathogen populations by conventional techniques is challenging in many of the environments where these diseases flourish, particularly as only limited diagnostics are available (*2*). Monitoring will likely become particularly difficult as prevalence is reduced (*3*). The power of molecular data to understand pathogen populations is already widely appreciated: Genetics can help confirm suspected cases, discriminate between strains, identify new infectious agents, understand the evolutionary history of populations, and shed light on transmission. For example, in the polio eradication campaign, a global network sequenced part of every virus isolated from around 200,000 stool specimens per year to identify transmission links and track the disappearance of particular genotypes (*4*). Genetic data identified polio outbreaks caused by oral vaccine–derived revertant strains, highlighting a need to gradually withdraw serotypes from the vaccine (*5*).

> ***"Genomic surveillance could thus be a powerful tool for tracking... parasite populations."***

Whereas the most comprehensive genetic data are for prokaryotes and viruses, most NTDs are caused by eukaryotic parasites that at least occasionally reproduce sexually. Most viruses and bacteria reproduce clonally, and exchange genetic material unpredictably, so molecular epidemiology can be restricted to tracking the abundance of different lineages through space and time. Recombination in sexual eukaryotes makes each region of the genome an independent genetic marker, so genomic data for a small number of individuals can reveal a great deal about the population those individuals come from. Genomic surveillance could thus be a powerful tool for tracking changes in the demography or abundance of parasite populations.

In many ways, the study of eradication genomics is a mirror image of conservation genomics. Although the latter aims to understand populations to preserve biodiversity and ultimately reverse species declines, eradication genomics studies the genetics of populations that are deliberately being reduced by human activity, to enhance our ability to depress the populations further and ultimately remove them completely. For some time, population genetic data have been used in conservation biology to understand changes in endangered populations (*6*), but we expect that analysis of eukaryotic pathogen populations could result in some important, more subtle lessons from conservation genomics. For example, that isolated subpopulations are harder to conserve implies that eradication will be easier if pathogen populations can be isolated from one another. In small populations, stochastic changes in allele frequencies due to random death or survival of individuals can swamp the natural selection of beneficial genetic variation; the increased impact of this genetic drift can make it much harder for small populations to adapt to changing environments. Furthermore, inbreeding within small isolated populations is expected to be deleterious (*7*). Looking for genomic signatures such as reduced genetic diversity and longer sequences of homozygosity due to inbreeding may therefore identify populations close to elimination (*8*) (see the figure).

One difficulty is that levels of genome-wide diversity in species can be strongly affected by life history and ancient demographic events, as well as recent changes in population size. We may thus need a good picture of pathogen populations before control measures have an impact. Therefore, collecting and conserving samples for genetic analysis should be an urgent consideration for control programs. Guinea worm is the parasite closest to eradication; cases have declined from several million per year in the 1980s to 30 in 2017 (*9*). However, Guinea worm infections were reported in Chad in 2011 after a decade with no reported cases. Coincident with this reemergence were infections in dogs, although Guinea worm was not previously considered zoonotic (*10*). We assume that Guinea worm evolved during the 10-year gap, but the lack of suitable samples predating 2011 makes it impossible to exclude the possibility that worms migrated from elsewhere during this time. Understanding the dog infections is key to the eradication program: Although there were only 25 human cases reported worldwide in 2016, more than 1000 dog infections were identified in Chad that year. The need to retrospectively obtain samples is clear. There are no historical Guinea worm samples stored

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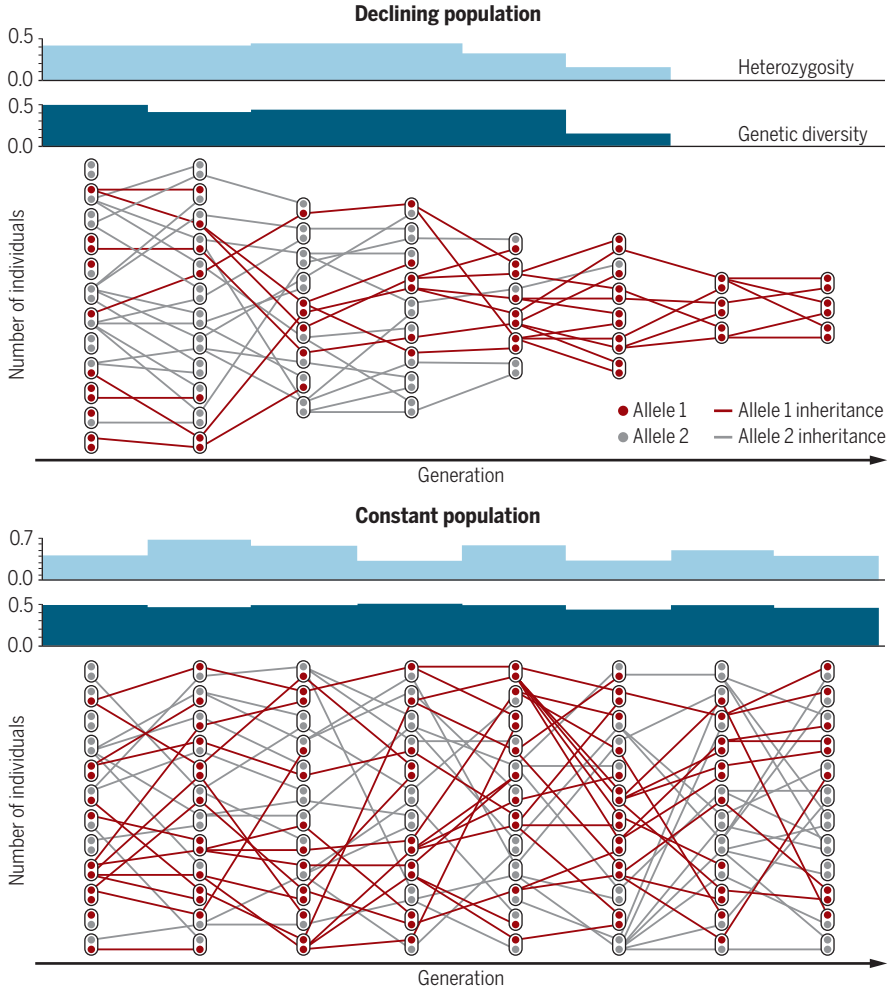
in a way that is likely to keep DNA intact, but there may be ways to circumvent the need for well-preserved DNA. Recent developments in paleogenomic methods, including improvements in the efficiency of building genomic libraries and the use of enzymatic treatments to reduce the impact of DNA damage, allow access to the highly fragmented and chemically modified genomic information recovered from archival specimens, and even from environmental sources such as archaeological specimens or sediments (*11, 12*). A precise picture of the historical population structure and size of these parasites will allow us to parameterize models of inbreeding and gene flow, improving the accuracy of inferences about the effect of control measures on current populations (*13*).

For many species, researchers have started exploring the genetics of populations using DNA "fingerprints" obtained from the differential distribution of microsatellites—repeat sequences in DNA—and other molecular markers. However, reductions in cost make whole-genome sequencing the most appropriate tool for the future, as genome-wide data are more powerful, and more comparable between populations and pathogens, and sequencing avoids the need to develop marker panels. At least for most key NTD pathogens, basic genomic resources such as annotated reference genomes are already available. Genome-wide data also enable the impact of control measures on pathogen populations to be understood beyond changes in distribution or numbers, as genomic data are sensitive to changes at functional loci and could reveal evolutionary changes of epidemiological relevance, such as the emergence of drug resistance. The emergence or sudden spread of new pathogen genotypes, signatures of strong recent selection on parts of the genome, or signs of a strong bottleneck in the absence of reduced prevalence are indications that a population is evolving in response to drug treatment or other control measures. This approach is being used to track artemisinin resistance in human malaria parasites in Asia, where population genomics approaches have played a key role in identifying the major locus responsible for reduced efficacy of the drug and understanding the genetic architecture of this trait (*14*).

Clearly, the highest priorities for control programs focus on delivering effective control measures and maintaining funding and political support. However, the rewards for collecting genomic data, and establishing pretreatment baselines through the analysis of archival samples, will be increasingly evident as programs mature. There will be many challenges in establishing genomic surveillance programs: the need to be comprehensive and coordinated, obtaining access to both prospective and archival samples, understanding the epidemiology and biology of the pathogens, to name a few. In some cases, theory will need to be developed to explain the population genetics of NTD pathogens, many of which have genetic systems distinct from those of obligately sexual, diploid animals. Translation of biomedical science to clinical practice has necessitated "bench to bedside" collaborations, and similarly, eradication genomics will require collaboration between technical experts in molecular biology and paleogenomics, as well as groups with expertise in the biology, control, and epidemiology of particular NTDs. The speed and scope of changes in NTD pathogen populations happening today is new territory for science. The ambitious goals set for NTD control will require pathogen populations to shrink at an unprecedented rate. However, success is not guaranteed (*15*) and will require constant vigilance. ■

Loss of diversity in a declining population

As control efforts reduce the size of a population, the chance that an individual is descended from closely related parents increases, leading to a decline in genetic diversity and heterozygosity.



Diagrams show inheritance of two alleles in simulated populations of 12 diploid individuals that declines or stays constant over eight generations.

GRAPHIC: ADAPTED BY A. KITTERMAN/*SCIENCE*

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