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Genomics and Novel Understandings of Infectious Disease

At first, the potential application of genomics to infectious disease do not appear as intuitive as its application to inherited disease. However, a great deal has changed within the past few decades in terms of the amount and quality of sequence information available and of the medical community’s awareness of its potential for use. In recent years, there has been a sizeable shift in perspective on the future of genomic medicine from solving genetic disorders to combating infectious disease.\(^1\)\(^2\)

Infectious disease has significantly and consistently affected civilization throughout recorded history, and continues to pose a nontrivial threat to people everywhere. From the bubonic plague, which spread from China and throughout Europe killing 25 million people, nearly a third of Europe’s population, in the mid-14\(^{th}\) century to the recent novel H1N1 swine influenza virus, which killed far fewer but nonetheless caused a significant pandemic scare and might have proved far more lethal, infectious disease epidemics have killed billions, with devastating, sometimes global, effects across nations.\(^3\)\(^4\)

\(^1\) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1363762/
\(^2\) http://content.karger.com/produktedb/produkte.asp?DOI=10.1159/000294170
\(^3\) http://www.themiddleages.net/plague.html
\(^4\) http://www.eyewitnessstohistory.com/plague.htm
Small mutations can transform a harmless strain of a virus into one that is highly virulent, but can also render a deadly virus innocuous. This knowledge can empower researchers to approach epidemiology differently in that they can at least partially account for the adaptability of disease in the development of vaccinations and the prediction of an epidemic's trajectory. In fact, advances in genomics have also yielded greatly improved methods of diagnostic testing for a variety of widespread diseases, especially after the sequencing of the human microbiome revealed information about many of the microbial species that normally can reside in the human body.

The advent of recent study of epidemics came about with the global outbreak of the SARS virus in 2003. People began to study the effects of travel on epidemics with vigor with a view to predicting their spread, but nonetheless, the technology required to sequence viruses rapidly did not exist at the time. Now, sequencing technologies evolve almost as quickly as the bugs they are used to sequence. Viruses like influenzas can recombine in new animal hosts to become highly virulent. For example, the Spanish Influenza of 1918-19, which killed an estimated 50 to 100 million people worldwide, was not, at first, as deadly as it became. It is believed now that the Spanish Flu started out as a solely avian virus, which then recombined with swine and human hosts in a sequence, a process which made the new form increasingly virulent. Its evolution may have helped fuel the unusual three-wave

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5 http://www.cdc.gov/sars/

6 http://wwwnc.cdc.gov/eid/article/12/1/05-0979_article.htm
structure of the pandemic’s evolution, with a second wave in the fall of 1918 that killed Americans at the rate of nearly 10,000 deaths per week.\footnote{http://www.pnas.org/content/96/4/1651.full}

At the time of the Spanish flu, of course, modern genomics and medicine really didn’t exist. In fact, doctors at the time believed at first that the mysterious disease was a ‘bacillus’, a small bacterium, although, now, of course, it is known to be a virus. Given its great historical impact (partly because of it coincided with World War I), the Great Pandemic is an interesting case to examine, both for its genomic sequence, which was completed in a few years ago,\footnote{http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm} and for its ethical and social significance in light of current genomic knowledge. Now we can sequence the genome of such a virus in order to more quickly identify it and work to create a vaccine.

A deeper understanding of how the Spanish flu recombined to form its more lethal strain would also be useful because nonepidemic Influenza A still kills an average of 30,000 Americans per year, many of them either elderly or infants.\footnote{http://jgv.sgmjournals.org/content/84/9/2285.full} Its descendants continued to be the only source of large and small scale epidemics until the H2N2 Asian Influenza in 1957. H1N1 viruses remained endemic in the swine population, sometimes resulting in animal-only pandemics, and resurfaced in later epidemics in the 1970s to which survivors of the Spanish flu had partial immunity.\footnote{http://wwwnc.cdc.gov/eid/article/12/1/05-0979_article.htm} The genome of the Spanish Influenza is still being studied to better understand
possible future epidemic threats. The study of these phenomena bloomed during the recent novel H1N1 swine influenza.

In fact, the novel H1N1 virus posed such a threat. The Spanish flu was so virulent in part because of it affected the host deep within the lungs and could spread easily from human to human and the reassortant H1N1 virus shared these features.\textsuperscript{11} Fortunately, novel H1N1 did not mutate into a stronger, more deadly form as the Spanish influenza did, with its case fatality rate of 2.5-10%.\textsuperscript{12} In the time that passed before researchers had developed and distributed an effective vaccine, the novel H1N1 swine flu could have easily mutated into a far more dangerous pandemic virus, killing many throughout the northern hemisphere before it spread in a second wave to the southern hemisphere.\textsuperscript{13} Deeper understanding of the genome of the swine flu and how it can adapt remains important.

Influenza viruses are not the only domain of application of genomics to infectious disease. Improved treatment can result from more genomic information about both the disease and the human genome and microbiome. The approach to influenza can be most improved by better knowledge of its own genome. In contrast, a better understanding of other diseases like the sexually transmitted Human Immunodeficiency Virus (HIV) requires a better grasp of the human genome and microbiome. As a consequence, HIV represents a case just as interesting as influenza

\textsuperscript{11} http://www.nejm.org/doi/full/10.1056/NEJMoa0903812
\textsuperscript{12} http://wwwnc.cdc.gov/eid/article/12/1/05-0979_article.htm
\textsuperscript{13} http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1000566
viruses for the understanding of the role of genomics in the treatment of infectious disease.

An estimated one million or more Americans are currently living with HIV/AIDS and it remains a global pandemic, making it a concern of high priority to both the medical and epidemiological communities.\textsuperscript{14} Its genomics has been an active research area for the past three decades and the interaction of this research and epidemic outcomes has made for substantial progress in the treatment of the disease. For example, information about humans with a tendency to be resistant to HIV has been applied to the development of pharmaceuticals.\textsuperscript{15} Understanding what genes are common to people with resistance help the pharmaceutical industry to develop drugs that mimic the effects of these genes, thus improving the lives of people who don’t have the necessary genes for resistance.

The HIV genome is by now fairly well understood. Using this knowledge, the HAART (Highly Active Antiretroviral Therapy) protocol has been developed and repeatedly improved upon, but there are still problems of antiretroviral resistance that prevent perfection of the protocol.\textsuperscript{16} Protease inhibitors, the most antiresistant drugs, require multiple mutations to create resistance, making these drugs more effective. Personalized genomic testing can make it possible to test patients for resistance to various drugs, which can eliminate the guesswork associated with the

\textsuperscript{14} http://aids.gov/hiv-aids-basics/hiv-aids-101/statistics/
\textsuperscript{15} http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2270331/
\textsuperscript{16} http://biochem118.stanford.edu/Projects/2012/Sebastian.pdf
decision as to which drug to prescribe so as to avoid drug resistance.\textsuperscript{17} The sequencing of the human microbiome can bring important information to bear on this issue, because we can now look at the sequence in humans that lends resistance to these antiretrovirals.\textsuperscript{18} HIV is not the only STI to which such a methodology could be applied, and if the likelihood that a patient would quickly develop resistance to medication could be minimized, that would represent significant progress in the treatment of infectious diseases.

Using genomics, the medical profession could approach infectious diseases in a whole new way that allows the development of personalized drugs and of vaccines that target the genetic sequence of incoming viruses – taking them out before they can even do damage as they replicate. In the case of infectious diseases, the use of genomics could speed the process of both problem identification and drug and vaccine development.\textsuperscript{19} It has already provided a far cleaner, more effective method of diagnosis than the use of cultures, which are messy and can yield incomplete and sometimes inaccurate information.\textsuperscript{20}

\begin{thebibliography}{99}
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The future of genomics and medicine is certainly not limited to studying genetic disposition to cancer and inherited disease. Indeed, the path of current research along the intersection of genomics and medicine is leading inexorably to its pervasive inclusion in epidemiology and public health, yielding both significant contributions to the literature and to society as a whole.