COMMENTARY

A Proposed Research Agenda for Ethical, Legal, Social, and Historical Studies at the Intersection of Infectious and Genetic Disease

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Over the past two decades there has been a rapid expansion in our understanding of how human genetic variability impacts susceptibility and severity of disease. Through applications of genome-wide association studies, genome and exome sequencing, researchers have made thousands of discoveries of genetic variants that impact risk of common and rare disorders affecting millions of people. Although these techniques have been primarily applied to highly prevalent chronic disorders such as diabetes[1] and cardiovascular disease[2], infectious diseases have proven to not be immune to genome-wide association, with studies of Tuberculosis[3], HIV[4] and SARS-CoV2[5], to name but a few, identifying host susceptibility loci across the genome. Unlike non-communicable diseases, infectious diseases have the unique element of impacting not only the affected the host, but those who may be most vulnerable to acquiring the infection. Thus, genetic variants that impact one individual's susceptibility to and severity of an infection may also have broader implications to public health, as was brought into keen focus during the COVID-19 pandemic. Therefore, as we begin to apply the knowledge gained from genomic studies in the clinic or into policy, there are unique ethical, legal, and social implications (ELSI) at the intersection of infectious diseases and human genomics. In this issue of the *Journal of Law, Medicine and Ethics*, Jose et al attempt to address this need by proposing a research agenda for ELSI studies at what they term the "blurred boundaries" of infectious and genetic diseases.[6]

The Johns Hopkins Center for Bridging Infectious Disease Genomics and Society (BRIDGES) began in 2014, focusing on the implications of genomic medicine in infectious diseases. Over the course of two years, and notably during the height of the COVID-19 pandemic, this "Research Collaboratory" conducted an agenda setting exercise involving a conceptual phase, aimed at identifying relevant case studies, and a deliberative phase to develop and refine the research agenda. This work resulted in the identification of 44 key research questions and proposes exploring those questions within identified themes, such as how genomic data affects disease conceptualization, the ethical implications of genomic information in clinical settings, public health strategies informed by genomics, and the social impact of genomic policies.

In the sections on conceptual framing and social policy, the authors, correctly in our view, focus on the potential negative impact of using genomic data to influence the meaning of infectious diseases, particu-

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larly where the associated genetic variants in question correlate with genetic ancestry. Should such situations not be handled with care, it is easy to imagine that the misuse of genomic data could exacerbate current health disparities and inequities faced by marginalized populations, including racialized groups. The "biologization of race," and its conflation with genetic ancestry, is an issue of much concern in the genomics community as a whole, as outlined in a recent report by The National Academies of Sciences, Engineering, and Medicine.[7] This is particularly important in situations where the movement of groups of individuals or their access to care may be restricted based on presumed genetic ancestry inferred from race. Careful consideration of the proposed research agenda would hopefully inform the development of laws and policies surrounding these issues prior to the next pandemic.

At the clinical level, the authors contend with the ethics of returning incidental, or secondary, findings to individuals undergoing genetic testing for some other primary purpose. This issue has received much attention and is not unique to genetic factors that impact infectious diseases. Indeed, the American College of Medical Genetics and Genomics[8] maintains a list of secondary findings that meet their criteria for reporting, as well as several policy statements outlining points to consider when determining if a gene or genetic variation meets the criteria of actionability with sufficient evidence to warrant reporting. The research agenda proposed by Jose et al support these established guidelines. Another intriguing area of focus of the research agenda is the potential dual role of the clinician in an infectious disease outbreak as both primary caregiver and public health practitioner. Whether knowledge of a person's genetic susceptibility to an infection would warrant rationing healthcare in times of scarcity is neither unprecedented nor unanticipated as a conceptual inquiry within the field. For instance during the COVID-19 pandemic, vaccines were diverted to groups at higher risk (e.g., seniors living in congregate settings, health care workers, and adults living in remote or isolated Indigenous communities) for severe outcomes while the supply chain struggled to meet demand. However, to do this with genomic data would require public buy-in, broad-scale knowledge of people's genome sequence, and a substantial amount of supportive evidence, much of which is currently not available.

Finally, the authors also highlight the need to determine the level of impact necessary for a genetic finding to be meaningfully predictive. Currently, the majority of genetic variants reported to influence the severity of common infectious diseases have relatively little predictive power at the individual level, generally far less than other sociodemographic, behavioral, and/or clinical factors, thus prohibiting them from being particularly clinically useful. There is also the practical consideration that, for the majority of the population, there is no genomic data available to use to make predictions, at least for now. There is some imaginable future where a persons' genome sequence becomes routinely collected medical information and thus, contending with issues of privacy, use and access sooner rather than later is a good idea.

There is no doubt that we will continue to gain insights into the impact of human genetic variation on infectious diseases as sequencing studies get ever larger. There is, sadly, also no doubt that we will again be faced with a pandemic causing pathogen, either known or unknown. At the intersection of this blurred boundary, being prepared to address the ethical, legal and social implications of using genomic data to improve public health must be a focus.

Overall, the authors bring to bear a highly multidisciplinary team of experts to develop several key questions of how we should consider using genomic data in the context of infectious diseases. Importantly, much of the research agenda they propose isn't unique to infectious diseases and may spark interest in the genomics community at large. However, one element missing from the discussions of the Research Collaboratory was the perspective of people with lived experiences that, in all likelihood, would be directly impacted by the answers to the questions they pose. Community involvement is critical when developing research questions, especially when it applies to key populations historically excluded from setting research agendas — as it appears to be the case here. Without their perspective, there is a risk of inadvertently perpetuating and re-enforcing stereotypes that depict certain populations as vectors of disease and widening

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the gap between research and practice for those who would benefit most from health innovations stemming from genomics. In our own work on the use of HIV genomic data to understand trends in transmission[9] we have found it incredibly useful to engage sex worker community activists to inform on the applications of genomics in infection prevention and control in Kenya in line with the Joint United Nations Programme on HIV/AIDS policy on the Greater Involvement of People Living with HIV.[10] Their involvement will undoubtedly translate into a more ethical and equitable application of HIV molecular epidemiology, the generation of data that is more informative for key population programs, and a greater mobilization of research participants in this context. This last point is especially notable, as genome-wide association studies, have generally struggled with diversity and inclusion.[11]

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Note

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