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

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Abstract: Contemporary understanding of the mechanisms of disease increasingly points to examples of "genetic diseases" with an infectious component and of "infectious diseases" with a genetic component. Such blurred boundaries generate ethical, legal, and social issues and highlight historical contexts that must be examined when incorporating host genomic information into the prevention, outbreak control, and treatment of infectious diseases.

Contemporary understanding of the mechanisms of disease point to a growing number of examples of "genetic diseases" with an infectious component and of "infectious diseases" with a genetic component. This overlap of what had formerly been understood as distinct categories of disease is noteworthy for both the change it signals in the understanding of disease mechanisms and the ethical, legal, and social implications (ELSI) it invokes. We refer to this phenomenon and its implications as "blurring boundaries." Although such reinterpretation of boundaries ought to influence our understanding of disease causation and gene-environment interactions, it is not clear whether or how much this will be the case. The blurring boundaries between infectious disease and genetic disease has implications for the boundaries that mark the intersections of public health, clinical care, and scientific research. Considerable research is required to better describe and understand the ELSI landscape of these blurred boundaries, ideally before host genomic discoveries are translated into infectious disease practice and policy.

The COVID-19 pandemic and the associated global research projects exploring host genomic modifiers of response to the infection caused by SARS-CoV-2 have brought into sharp relief the need to identify, study, and respond to the ELSI issues and historical

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contexts — for individuals, groups or the larger society — of using genomic information in the management of infectious disease[1]. The Johns Hopkins Center for Bridging Infectious Disease, Genomics, and Society (BRIDGES) — a Center for Excellence in ELSI Research — was established to examine the ethical, legal, social, historical, and policy issues confronting the incorporation of genomics in the prevention, outbreak control, and treatment of a range of infectious diseases. In this paper, references to infectious and genetic diseases are meant to include a range of infectious and genetic conditions, whether or not they rise to the level of a disease classification.

As part of the BRIDGES exploration of these issues, we formed a "Research Collaboratory" to craft research and policy agendas that clarify the implications of the blurring of boundaries and the merging of scientific categories that were previously distinct. One product of that work is a proposed research agenda for ethical, legal, social, and historical studies that identifies the most pressing —and intriguing — unanswered questions raised at and by the blurring boundaries. We hope that others will begin to pick up and address these issues in anticipation not only of further blurring boundaries, but also future pandemics and relevant genetics research.

Background

BRIDGES began in 2014 with a focus on the ethical, legal, social, and policy significance of communicable disease transmission, and variation in the modes and patterns of transmission among diverse communities and populations, with an eye toward reducing disparities in infectious disease burden. This work included three pilot projects focused on these three discrete but related program areas: (1) Research, (2) Public Health Policy, and (3) Clinical Practice. The pilot projects studied the implications of implementing genomic medicine in the infectious disease context in each of these three areas, using a specific infectious disease as an example. The first project assessed the ELSI impact of research on genetic variation in the transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in cohorts of at-risk urban populations[2]. The second project analyzed the role and impact of advances in "vaccinomics" for informing population-based prevention of infectious diseases such as pandemic influenza[3]. Vaccinomics is the application of

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genomics in improving the development of vaccines and studying host response to vaccines[4]. The third and final pilot project assessed the application of genomics in the clinical management of acute, high consequence infections such as Ebola and Methicillin-resistant Staphylococcus aureus (MRSA)[4].

The BRIDGES Center consists of an interdisciplinary group of co-investigators, consultants, trainees, and members of an Internal Advisory Board. These groups include experts from the fields of history, law, philosophy, applied ethics, genetics, and medicine, in addition to ELSI experts. Sub-teams were formed around particular disciplines or topics, including historical analysis and legal issues; woven throughout all three of the pilot projects was cross-cutting history and legal scholarship. The BRIDGES history team investigated biocontainment in the historical context of infectious disease control and the genetic modification of nonhuman species for public health purposes[5]. The BRIDGES legal team examined whether genetic testing for variants associated with influenza infection should be mandatory for healthcare employees and whether there are legal obstacles to accessing and using genetic information from biobanked research samples for infectious disease research[6].

Taking advantage of the infrastructure and relationships created in these pilot projects, the BRIDGES team (comprised of the authors of this paper) focused the next phase of the project on crafting an ELSI research agenda outlining work that remains to be done. This phase coincided with the COVID-19 pandemic, which has seen unprecedented levels of international collaboration and coordination to identify host genomic factors involved in COVID-19. The global COVID-19 Host Genetics Initiative was launched early on in the pandemic with the aim of bringing "together the human genetics community to generate, share, and analyze data to learn the genetic determinants of COVID-19 susceptibility, severity, and outcomes"[7]. This pandemic, coupled with advances in genomic sequencing technology, has provided a global laboratory for identifying host genomic factors that might play a role in COVID-19 transmission, infection, and/or severity. The identification of such factors has implications for both clinical management and public health practice. In 2020, Geller *et al.* published on the ethical implications of using COVID-19 host genomics for clinical and public health practice as the current pandemic "provides an opportunity to move from theory to action in a very real context"[8]. The article highlighted some of the ethical questions that need to be considered before using host genomic information to inform decision-making in the clinical, public health, and health workforce settings. Similar kinds of information, such as non-genomic risk factors and vaccination statuses, are already being used to make decisions about resource allocation[9], insurance coverage[10], and travel restrictions[11]. Before host genomic information is added to this list, it is important to investigate a broad range of ELSI issues, from conceptual or framing issues to more concrete questions related to clinical practice, public health policy, and social policy, as described below.

Methods

The BRIDGES team planned and facilitated a collaborative, interdisciplinary research agenda-setting exercise over the course of two years. This exercise involved two key stages: (1) conceptual and (2) deliberative. The conceptual stage was primarily focused on conducting a series of literature reviews and generating case studies. The deliberative stage of the project focused on forming the Research Collaboratory, facilitating the Collaboratory meetings and the collective, iterative development of the research agenda.

Stage 1: Conceptual

During this first stage, the main aim was to characterize the relationship and boundaries between infectious and genetic diseases, examine the historical context of this distinction, and explore the implications of the changing and overlapping nature of these boundaries for ELSI discourse, scholarship, and translation. The BRIDGES team met on a monthly basis to define the scope of the project, identify key search terms, conduct literature reviews across the historical, philosophical, legal, ethical, and social terrains at this intersection, and generate a set of infectious disease and host genomics case studies to be used in the deliberative stage. The history and philosophy team explored the historical literature to identify examples of blurring boundaries between infectious and genetic diseases and how the nature of those blurring boundaries have changed over time. The bioethics and legal team reviewed the relevant ELSI literature. In addition, the legal team examined the legislative history of GINA, the potential use of genetic information by public health officials, and vaccine injury compensation. These reviews identified examples of blurred boundaries in science and medicine with an ELSI lens and specific cases for informing the deliberative process.

Informed by these discipline-specific literature reviews and analyses, we generated six brief candidate case studies that represent a range of interdisciplinary topics at this blurred boundary. These cases would serve to catalyze and frame the discussions in

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the deliberative stage. The six selected case studies were based on different infectious diseases with demonstrated or likely host genomic components. The cases include: (1) COVID-19 caused by SARS-CoV-2, (2) acquired immunodeficiency syndrome (AIDS) caused by HIV, (3) hepatitis C, (4) Ebola, (5) Zika, and (6) tuberculosis (TB). These cases were selected to capture a broad range of infectious disease characteristics, host genomic findings, histories, and ethical issues. The cases vary in terms of the mode of transmission, the clinical and public health implications of the host genomic variants, the legal issues raised, and a variety of other historical and contextual factors including stigma associated with the disease, treatment cost, availability of effective treatments, and resource allocation. Each case study included a one-page description with information on the science of the infectious disease and host genomics as well as a context section that highlighted the key cultural, historical, and/or legal contexts associated with the specific infectious disease. These case studies along with the other materials synthesized during this conceptual stage informed the deliberative stage of the research-agenda-setting exercise.

Stage 2: Deliberative

In this next stage, the main aim was to leverage the infrastructure and relationships created in Phase 1 of BRIDGES to bring together colleagues working at the intersection of infectious disease and genomics for a series of planning and working group meetings of a Research Collaboratory. The deliberative stage consisted of three parts: (1) forming the interdisciplinary Collaboratory, (2) facilitating the two Collaboratory Meetings with the goal of drafting the preliminary research agenda, and (3) refining the case studies and the research agenda.

Forming the Collaboratory

An invitation list of key experts across a diverse range of disciplines was formed. Based on prior research, our target disciplines were bioethics, ELSI, genomics, history, infectious disease, law, philosophy, and public health. This list of invited Collaboratory members consisted of experts both internal and external to Johns Hopkins University. The final Research Collaboratory included 15 outside experts and all 16 members of the BRIDGES team.

Collaboratory Meetings & Preliminary Research Agenda

Two Collaboratory Meetings were organized. Due to the COVID-19 pandemic, both 3-hour meetings were hosted virtually via zoom. Collaboratory Meeting 1, titled "Horizon Scanning of ELSI Issues Relevant to the Blurring Boundary Between Infectious and Genetic Diseases," was held in 2020; while Collaboratory Meeting 2, titled "Development of an ELSI Research Agenda Relevant to the Blurring Boundary Between Infectious and Genetic Diseases," was held in 2021.

Collaboratory Meeting 1

The main goal of the first meeting was to develop a broad list of ELSI issues relevant to the blurring boundaries and select two case studies (of the six short cases presented and discussed) as a focus for the second meeting. In advance of the first meeting, Collaboratory members were sent the six short cases and a list of discussion prompts to stimulate thinking about the various ethical, legal, social, historical, and policy considerations that may arise in the public health, clinical, and research contexts. These prompts were extracted from a prior BRIDGES publication which had identified various contexts both in COVID-19 and other infectious diseases in which host genomic data could be used[12]. Collaboratory members were given a brief background on current knowledge regarding the host genomics' underlying response to infection in the cases referenced above. These short presentations were intended to introduce participants to the scientific concepts relevant for the discussions. Following this introduction, the large group discussed the SARS-CoV-2 case to identify a list of ELSI issues and historical antecedents specific to the potential use of host genomics in employment, public health, clinical care, and other contexts. The other five case studies were divided among three small breakout groups. Each group was tasked with identifying ELSI issues specific to each of their assigned cases. During these discussions, human papillomavirus (HPV) emerged as a possible case study, given its role in the development of non-communicable diseases (i.e., cancers). The HPV/Cancers case highlighted a unique case of the blurring boundary of infectious and genetic diseases. After a series of large group discussions, the Collaboratory selected SARS-CoV-2/COVID-19 and HPV/Cancers as the two final case studies for further development to aid with the generation of the research agenda at the second meeting.

These two cases were used to represent two ends of the spectrum of the blurring boundary between infectious and genetic diseases and come with very different cultural contexts. The SARS-CoV-2/COVID-19 case is an example of a primarily infectious or communicable disease that has host genomic features. The initial case

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was expanded to highlight structural racism in the US, as the pandemic continues to disproportionately impact historically marginalized populations, and the need to understand that the racial inequities in morbidity and mortality are due to underlying social inequalities rather than innate biological differences between the groups. The HPV/Cancers case was created as an example of a primarily non-communicable disease with an infectious agent as a primary cause. This case highlights the context of sexuality and the disproportionate focus of HPV awareness and vaccination among women and girls, with substantially less engagement with boys and men who can also carry and transmit HPV to sexual partners. These two expanded case studies were shared with Collaboratory members in advance of the second meeting.

Collaboratory Meeting 2

The main goal of the second meeting was to develop an ELSI research agenda based on the two selected case studies. The Collaboratory was split into two small, intentionally interdisciplinary breakout groups that met twice to generate a more comprehensive list of research topics and questions. Collaboratory members were encouraged to identify research questions across the various disciplines represented in the group and potential contexts for the use of host genomic information. The lists of research questions identified in each group were then compiled and deduplicated to develop the preliminary version of the research agenda. Following this meeting, the preliminary research agenda was shared with the Collaboratory members for further input on each of the questions and to add any questions that may have been missed.

Refining the Case Studies and the Research Agenda

Building on the discussion at the Collaboratory meetings, BRIDGES held a series of internal team discussions to revise, expand, and further analyze the two selected case studies and the research agenda questions. Over the next six months, the team met biweekly to examine the gaps in the case studies and research agenda questions. Both the SARS-CoV-2/COVID-19 and HPV/Cancers cases were revised to include more of the global impact of the diseases as well as issues related to vaccinomics. The context sections of both cases were also expanded to include additional historical research. For example, these contexts include how racism and sexism have and continue to shape the response to SARS-CoV-2/COVID-19 and HPV/Cancers, respectively.

After finalizing the case studies (see Supplements 1 and 2 for the final case study documents), the team refined the preliminary research agenda based on the feedback from the Collaboratory members and spent multiple rounds workshopping the framing and organization of the research questions.

Results — Research Agenda

The Research Collaboratory identified 44 research questions that we have categorized under four broad themes, listed below. It's important to note that the questions could have been categorized in many different ways, such as by specific topic areas (i.e., vaccine, employment, disparities, etc.), types of policies (i.e., social, public health, etc.), or discipline (i.e., history, science, legal, etc.), and in fact may fit rationally in multiple categories given the blurring boundaries. We ultimately landed on conceptual framing and knowledge interpretation and three sets of topical questions (clinical practice, public health policy, and social policy) due to the centrality to this whole project of the blurring boundaries concept, the subsequent conceptual shifts at that boundary identified through our work, and the desire to organize the remaining questions in a way that highlights the value and importance of interdisciplinary work amid such conceptual shifts. Academics, funding organizations, and others will need to address these questions as we move towards the implementation of host genomics in the infectious disease context. These stakeholders can also recategorize the questions in ways that are most useful and informative for them. Below, we highlight a subset of the 44 questions that generated considerable discussion among the Research Collaboratory members and serves to illustrate the intersections, overlaps, and synergies among all the questions. We provide additional information regarding the historical context and the motivation for those specific research agenda questions within each of the four categories. The order of the questions was decided based on narrative flow and not priority.

Theme 1: Conceptual Framing and Knowledge Interpretation

This first category of research agenda questions centers on how to best understand different claims about the blurring boundaries concept, disease causation, and their associated social meanings. The first research agenda question in this category (see Q1 in Table 1) asks: *What kinds of* ***social interests have influenced*** *different stakeholders' views of (blurring boundaries)* ***disease causation*** *in the past, including causes related not only to infectious agents and*

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host genomics, but also social determinants of health (SDH)? This question involves exploring the large and rich historical literature on disease causation to identify why certain factors were highlighted as causative over other factors. Social interests and factors may have influenced different stakeholders in adopting a narrower view of disease causation and focusing on perceived scientific causes rather than a multidimensional view of disease causation. For example, early in the HIV/AIDS epidemic, hemophiliacs, injection drug users, Haitian immigrants, and the gay community were recognized as major risk groups[13]. The members of these groups, known colloquially, and denigrated as, the 4-H club, were stigmatized as the primary agents of disease spread while their belonging to these groups rendered them at-risk of persecution and also unable to donate blood[14]. Moralistic and derogatory narratives about injection drug users, members of LGBTQ communities, and racial minorities led to highly discriminatory disease surveillance policies that served to advance certain social and political interests and further marginalize these groups. Such framing also contributed to a lack of knowledge of, and the motivation to address, the root causes of HIV as well at its manifestations in other at-risk groups, including women. The case of HPV-related cancers demonstrates related dynamics with regard to women's sexuality and race. Nineteenth century theories about cervical cancer causation supported the idea that women were more physically vulnerable and defined by their sex organs, assumptions that justified their confinement to the domestic sphere[15]. The low rate of cervical cancer observed in Jewish populations has also been used to support the idea that racial categories are biological[16].

The racialization of disease evidenced in HIV and HPV histories is not unique to infectious disease. In the genomics context, race is often treated as a proxy for genetic ancestry[17]. Expert claims about the hereditary basis of race, intelligence, crime, and even unemployment pre-date and continue with the emergence of genetic science[18]. For example, the eugenics movement heavily relied on the biologization of race and in turn, helped create and reinforce racial hierarchies[19]. These narratives have contributed to the false belief that race is biological.[20] In the case of host genomics, researchers may discover genetic variants that occur in high frequency in particular ancestry groups. Such discoveries pose a significant risk of being interpreted as demonstrating fixed biological differences between different race/ethnicity groups and reviving/reinforcing the biologization of race[21]. Thus, in part due to what we have learned about the history of notions of disease causation, these findings need to be communicated with care (see Q7 in Table 1): *How should researchers talk about the* ***real (if probabilistic) differences*** *across populations with different ancestries without reifying social constructs, and while appropriately attending to social determinants of health, including the* ***impact of racism****, on infectious disease exposure and outcomes?* When ancestry-associated host genomic risk factors are identified in infectious disease susceptibility or severity, it is critical to balance these factors with the non-genomic risk factors, such as SDH and racism, that play a role in preexisting health status, infectious disease exposure, and health care access.

One of the ways in which these multiple risk factors can be balanced is by taking into account the predictive value of genetic variants. Predictive value is the likelihood that a person will develop the phenotype if they have the mutation of interest; this is complicated in host genomics of infectious disease, because exposure to the infectious agent is required. And exposure is determined by a range of non-genetic factors, including many social determinants of health. Thus, even in the context of a high predictive value genetic variant, if an individual is able to avoid exposure, the genetic risk is immaterial. This raises the broader issue of what kinds of actions are taken given different levels of predictive value for genetic variants, highlighted by the research agenda question (see Q9 in Table 1): *What factors (clinical, scientific, social) determine what counts as a "****meaningful" level of predictive value for genetic variants*** *across infectious and non-infectious disease contexts, where "meaningful" relates to clinical, public health, or personal utility and the opportunity costs inherent in the (public) investment required to find such genetic variants?* There may not be one level of predictive value that could be applied to all genetic variants or infectious diseases. Since the boundary between the two categories of disease is blurring, other related factors, such as the mode of transmission, the infectiousness of the disease, and the health consequences of the disease need to be considered and they may determine the level of predictive value that makes a mutation's predictive value meaningful. For example, there may be instances where genetic variants with low predictive value are found for a high consequence infectious disease and/or variants with high predictive value but for a low consequence infectious disease. These scenarios raise questions about when it is appropriate to use host genomics in the infectious disease context, what the consequences are of not having a single threshold for predictive value, what counts as a meaningful level of predictive value, and who should decide these thresholds?

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Theme 2: Clinical Practice

This category includes research questions about the use of host genetic testing in clinical practice when a test becomes available that helps predict an individual's response to an infectious disease or vaccine. There are several normative research questions about law and policy that are also raised in this category, such as whether medical providers should be permitted to or prohibited from reporting parental neglect in the case of not vaccinating a child who is at a greater genetic risk

Table 1

Conceptual Framing and Knowledge Interpretation Research Agenda Questions

Conceptual Framing & Knowledge Interpretation Questions	
Q1	What kinds of **social interests have influenced** different stakeholders' views of (blurring boundaries) **disease causation** in the past, including causes related not only to infectious agents and host genomics, but also social determinants of health (SDH)? Historically, how and why do certain social factors influence different stakeholders' views of blurring boundaries around disease causation, including causes related not only to infectious agents and host genomics, but also to modifiable SDH?
Q2	What are the historical changes in the **understanding of disease causation** (e.g., in HPV: girls vs. boys, behavioral changes, smoking-related head/neck cancer vs. HPV-related cancer)?
Q3	How does the changing understanding of what causes a disease (e.g., cervical cancer) affect **stigma**? Does the emergence of genetic risk factors or an "infectious" cause alter stigma in any way? What if the genetic risk factors vary across populations?
Q4	Cases of blurred boundaries involving **cancer** take on a third layer of cultural baggage beyond our beliefs and practices regarding genetic and infectious diseases. How do professional and public attitudes about cancer influence the drawing of the genetics/infectious boundary in these cases? How do historical and cultural narratives of **cancer, infectious disease, and genetics intersect** — what are their similarities and differences?
Q5	How should we think about **an infectious disease with respect to causation** in a virus-associated cancer?
Q6	How will research at the intersection of genetic and infectious disease shape the ongoing evolution of disease classification as well as definitions of **"normal" and "pathological"**? Should rare genetic variants which convey infection resistance be considered the optimal state of health and the far more common susceptibility variants be seen as correspondingly pathogenic, or should vulnerability to infection be seen as the normal human condition? What would be the ethical, social, and practice implications of interpreting things one way or the other?
Q7	How should researchers talk about the **real (if probabilistic) differences across populations** with different ancestries without reifying social constructs, and while appropriately attending to social determinants of health, including the impact of racism, on infectious disease exposure and outcomes?
Q8	What **meaning is given to these real (if probabilistic) differences across populations** in our medical/social/scientific explanations of disease?
Q9	What factors (clinical, scientific, social) determine what counts as a **"meaningful" level of predictive value for genetic variants** across infectious and non-infectious disease contexts, where "meaningful" relates to clinical, public health, or personal utility and the opportunity costs inherent in the (public) investment required to find such genetic variants?
Q10	What implications for policy and practice (across contexts and actors) would flow from a finding that the **genetics of a stigmatized noncommunicable condition (e.g., obesity) plays a bigger** role in infectious disease susceptibility than the host genetics related to a specific infectious disease?
Q11	How should knowledge about genetic and/or physiological susceptibility influence beliefs about **public health duties** (e.g., wearing masks)? How should it shape individuals' evaluation of their own public health duties?
Q12	If risk factors for noncommunicable diseases can be **transmitted horizontally** (e.g., microbiome), how does it impact people's understanding and public health authorities' communication about risk and how/whether individuals change their behavior in response to that transmission risk?
Q13	How have social interests, historical trajectories, and assumptions about the kinds of phenomena that are legitimate objects of study **shaped the funding landscape** (and thus the type of research that is done) at the genetic and infectious disease interface?

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of infectious disease susceptibility (see Q15 in Table 2) or notifying affected individuals of relevant incidental genetic findings in the infectious disease context (see Q19 in Table 2). If genetic variants are found to play a role in increased severity of an infectious disease and are determined to have meaningful predictive values, then a host genetic test may be developed to identify individuals who are at greater risk of severe disease and/or adverse outcomes. For example, in the COVID-19 case (see Supplement 1), several genome-wide association studies have identified and replicated the finding of genetic variants in a gene cluster on chromosome 3 that are associated with COVID-19 hospitalization and/or severity[22]. These host genomic findings could inform the allocation of scarce resources, such as vaccines or treatments. If vaccines, medications, or treatments are scarce during an infectious disease outbreak, healthcare institutions could decide to allocate doses only to those individuals who are at a higher genetic risk of adverse response to vaccines or outcomes from the infectious disease, in an effort to conserve resources.[23] Such a public health policy would necessarily be implemented by physicians, whose duty is to the patient in front of them, creating a potential conflict. For example, physicians may need to withhold vaccine doses from patients who are not at genetic risk for severe disease and/or from those who may be genetically resistant to the infectious disease. These cases highlight the research agenda question (see Q14 in Table 2): *How should the issues raised by the **dual roles of physicians** as both clinician and public health provider in the context of vaccine decision-making be addressed in policy and practice?*

Another clinical practice question is related to cases where physicians may not have a choice but to inform their patients of incidental host genetic findings related to infectious disease. The area of incidental genetic findings has been fraught with debates on whether or not providers have legal or ethical duties to notify patients of such findings[24]. The same question is raised in the infectious disease context (see Q19 in Table 2): *Do laboratories, health care providers, and/or others have a heightened **duty to notify** individuals of **incidental genetic findings** that have implications for infectious disease transmission, severity, immunity, and/or treatment?* Genetic findings in this context can also include ***pharmacogenomic** (**PGx**) information which may be used in the clinical treatment and public health reporting of infectious disease. What are the implications of pleiotropy (when a particular genetic variant has implications to more than one trait/condition) at this intersection?* (see Q16 in Table 2). In addition to questions about a provider's duty to notify, this may also result in patients knowing about their risk and/or outcomes for both diseases without the choice of knowing about just one of the diseases. Thus, a patient's right not to know could also be implicated in the cases where there is pleiotropy[25].

Table 2

Clinical Practice Research Agenda Questions

Clinical Practice Questions	
Q14	How should the issues raised by the **dual roles of physicians** as both clinician and public health provider in the context of vaccine decision-making be addressed in policy and practice?
Q15	When a child carries a genetic variant that predisposes them to greater infectious disease susceptibility or severity, and the child's parent(s) **choose not to vaccinate the child**, should that action be considered as neglect that requires the parents to be reported to a relevant government agency for intervention?
Q16	What would be the implications of incorporating **pharmacogenomic (PGx)** and other information on host genetic variation in the clinical treatment (and public health reporting) of infectious diseases? Specifically, what are the implications of pleiotropy (when a particular genetic variant has implications to more than one trait/condition) at this intersection?
Q17	Are there **host genetic determinants** that explain why a virus-associated cancer like HPV-related head/neck cancer has **better prognosis** than non-virus-associated cancer? If so, what are the ELSI implications of that fact?
Q18	We are in an era when genetic information is not yet well integrated into **electronic health records** (EHRs) (e.g., genetic test results are usually uploaded as scanned PDFs), and few patients have had any genetic testing. The future is likely to include much more genetic information in EHRs. What are the implications for access to and use of this information in the context of infectious diseases? What should we do with host genomic information now, given how it might be used in the future?
Q19	Do laboratories, health care providers, and/or others have a heightened **duty to notify** individuals of **incidental genetic findings** that have implications for infectious disease transmission, severity, immunity, and/or treatment?

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Theme 3: Public Health Policy

This third category includes research questions about what public health programs should do in relation to the use of host genomic information in screening, surveillance, vaccination, and other public health interventions for infectious disease. If the infectious disease outbreak is also declared as a public health emergency at the state or national level, then there is an additional layer of policy implications for using host genomic information in that context. Similar to the clinical practice question of a physician's duty to notify individuals of host genetic findings, the same findings may also need to be reported to public health authorities in the case of an infectious disease outbreak. States might wish to require mandatory reporting of host genetic findings, which, subject to legal analysis, could further blur the line between clinical care and public health. Infectious diseases

Table 3

Public Health Policy Research Agenda Questions

Public Health Policy Questions	
Q20	Should infectious disease reporting laws require laboratories, health care providers, and/or others to **report genetic test results** to public health authorities when those results suggest that an individual has greater susceptibility to infectious disease or greater likelihood of severe disease?
Q21	What issues may arise in identifying host variants associated with **different degrees of vaccine efficacy in different populations**? For example, in 5% of cases, the current COVID-19 vaccines are not effective. If there are host genetic components that are related to vaccine effectiveness, what is the significance for public health policies?
Q22	How might genetic information inform decisions related to no-fault compensation for **vaccine injuries**?
Q23	Is it legally permissible to **prioritize vaccination** for individuals who have a genetic variant that predisposes them to greater susceptibility and/or severity of infectious disease? Conversely, is it legally permissible to deprioritize for vaccination individuals who have a genetic variant that predisposes them to immunity to infectious disease?
Q24	Should individuals who have genetic variants that predispose them to immunity be able waive out of **vaccination mandates**?
Q25	If we were to identify genetic variants that increase one sex's susceptibility to (e.g., girls' likelihood of converting to persistent HPV) or transmission of (e.g., boys' likelihood of transmitting HPV) a sexually transmitted disease, how would **social attitudes about sexuality** be affected?
Q26	Should **newborn screening** include genetic testing related to infectious disease susceptibility, severity, and/or immunity? If so, would any changes need to be made to existing privacy and newborn screening laws? If a screened genetic condition is associated with greater likelihood of infectious disease transmission, should a public health authority be able to use that information in disease management?
Q27	Should the law hold individuals who have knowledge that they are "**super-spreaders**" due to a genetic variant criminally and/or civilly responsible for disease transmission?
Q28	Should federal and state authorities be allowed to **waive the Genetic Information Nondiscrimination Act (GINA)'s genetic privacy provisions** to protect public health? If so, under what conditions? To whom can such information be disclosed?
Q29	Should public health authorities have the legal power to **mandate genetic testing** related to infectious disease during a public health emergency?
Q30	What laws, if any, prevent or facilitate the use of genetic information to **regulate the movement** of specific individuals?
Q31	As the definitions of genetic and infectious disease have changed over time, how has (presumed) genetic and/or infectious disease risk information been used to **limit movement in the past**?
Q32	Could **incentives** for participation in public health interventions such as vaccination also be applied to genetic testing for relevant host genomic variants?
Q33	Should individuals be permitted to use their personal genetic information from **direct-to-consumer (DTC)** or other types of genetic testing to exempt themselves from public health interventions? Would research into individual risk factors undermine collective approaches to reduce disease burden in the population through public health interventions (e.g., vaccination)?

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have an impact both at the individual and population level and as such, any host genetic findings related to an infectious disease has implications for both the individual patient and public health. Consequently, *when an individual's genetic test result suggests that they have greater susceptibility to infectious disease or greater likelihood of severe disease, should infectious disease reporting laws require laboratories, health care providers, and/or others to* ***report genetic test results*** *to public health authorities?* (see Q20 in Table 3).

While the above question deals with genetic tests that take place in a traditional clinical setting, there may be public health implications when individuals choose to learn about their own host genomic risk related to infectious disease through **direct-to-consumer** (**DTC**) or other similar types of personal genetic testing. *Should individuals be permitted to use their personal genetic information from DTC or other types of genetic testing to exempt themselves from public health interventions? Would research into individual risk factors undermine collective approaches to reduce disease burden in the population through public health interventions (e.g., vaccination)?* (see Q33 in Table 3). If an individual finds that they are at a much lower genetic risk of severe infectious disease, should they be permitted to use that result to exempt themselves from quarantine or social distancing measures? This question has broader implications for host genomic research as well. Traditional public health interventions rely on the cooperation and collective action of communities, which may be undermined if individual risk and preferences serve as exemptions from public health measures. On the other hand, can or should public health authorities use host genetic risk to target certain public health interventions? As the research agenda question asks, should *law prevent or facilitate the use of host genetic information to* ***regulate the movement*** *of specific individuals?* (see Q30 in Table 3). For example, genetic passports could be used to implement quarantine or isolation policies based on host genetic information rather than infectious disease exposure or a documented infectious disease diagnosis[26]. The answer to this question may be informed by studying *how (presumed) genetic and/or infectious disease risk information has been used to* ***limit movement****, such as immigration restrictions, in the past* (see Q31 in Table 3). Historical analyses could provide important insight into how the use of host genomic information to target interventions among at-risk groups can be balanced with the ideas of collective action and solidarity emphasized in traditional public health measures.

Theme 4: Social Policy

Social policy issues such as discrimination, privacy, and the biologization of race also arise at the blurred boundaries between infectious and genetic diseases.

One of the most important social policy questions regards the harmful *impact of using host genomic information on the concept of biologization of race* (see Q36 in Table 4). While race is often constructed as hereditary, it is without biological significance and is rooted in racial scientific constructions of difference most often linked to phenotypical characteristics as well as stereotyping. If and when genetic variants in infectious diseases are found to be highly prevalent among individuals with a shared genetic ancestry, safeguards should be in place to resist the stratification of the population based on race and ethnicity.

Biomedical research in both genetic disease and infectious disease has a legacy of biologizing social categories of race and ethnicity. For example, racial disparities in epidemic disease have been blamed on perceived differences in the biologies or behaviors of racial and ethnic groups as illustrated by the earlier example of the certain identified groups during the HIV/AIDS epidemic[27]. In the case of COVID-19, to date there has been an insistence that differences in disease outcome must be understood in structural terms, as social rather than biological phenomena. At the same time, there are calls for increasing participation of minoritized populations in both genomic and vaccine research, which are often justified in terms of biological differences[28].

The genomics community is actively grappling with the use of race, ethnicity, and ancestry as population descriptors in genomics research[29], bringing us to the question(s): *What social policies might help future research into genomics of susceptibility not collapse into yet another* ***biologization of racial and ethnic differences****, and at the same time avoid exclusionary "color-blindness" in the design of scientific research? And what role can bioethics and public health researchers play in advancing this discussion and preventing the conflation of racism, race, social determinants, ethnicity, and ancestry within the context of public health?* (see Q36 in Table 4). It is important for the bioethics and public health research communities to learn about and become involved in these efforts so as to ensure that host genomic findings associated with genetic ancestry do not reinforce the biologization of race.

While understanding the links between disease risk and genetic ancestry may improve health outcomes, it is also important to recognize the threats posed by the implementation of public health policies using that

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knowledge[30], for example, if inappropriate causative weight is attached to correlations between genetic variants and race/ethnicity by both the public and public health officials. This threat is highlighted in the following research question: *if there is a genetic variant associated with infectious disease transmissibility (e.g., **super-spreader**) that positively correlates with a particular racial and/or ethnic group, should public health officials have the legal authority to restrict the movement of members of that group to stem the transmission of disease during a public health emergency?* (see Q37 in Table 4). Such questions raise issues of genetic discrimination and *whether members of the targeted group can contest the infringement on their liberty on any legal grounds* (see Q37 in Table 4). If public health interventions are targeted at specific groups based on genetic ancestry, it is possible that those interventions could be construed as discriminatory, given that genetic ancestry is often used as a proxy for race/ethnicity[31]. Thus, it is critical for the concept of genetic ancestry to be disentangled from the socially constructed concepts of race and ethnicity before implementing policies that target individuals from a genetic ancestry group who have merely a

Table 4

Social Policy Research Agenda Questions

Social Policy Questions	
Q34	How do we manage the **conflicts** that arise among the areas of research, clinical activity, infection control, and public health operations, which are ongoing and likely to increase moving forward?
Q35	Has the immunology we use to model/develop vaccines been **biased** by a hundred years of **research by/among Europeans** (or the structurally privileged), perhaps optimizing vaccines for Europeans (the structurally privileged)? As a result, could vaccines initially be undermined in populations that are a majority outside of the United States? Similarly, different animal (e.g., mouse) species (or strains in case of mice) have different immunological characteristics that more or less align with "normal" human responses. To what extent have animal models been "validated" based on European (or male) immunology (potentially an example of a structural bias)?
Q36	What social policies might help future research into genomics of susceptibility not collapse into yet another **biologization of racial and ethnic differences**, and at the same time avoid exclusionary "color-blindness" in the design of scientific research? What role can bioethics and public health researchers play in advancing this discussion and preventing the conflation of racism, race, social determinants, ethnicity, and ancestry within the context of public health?
Q37	If there is a genetic variant associated with infectious disease transmissibility (e.g., **super-spreader**) that positively correlates with a particular racial and/or ethnic group, should public health officials have the legal authority to restrict the movement of members of that group to stem the transmission of disease during a public health emergency? On what legal grounds can members of that group contest the infringement on their liberty?
Q38	Should public health authorities have the legal power during a public health emergency to **compel individuals to provide biomaterial** that, based on their genetic information, is likely to contribute to the development of essential preventives and treatments?
Q39	Do current human subjects research regulations permit the public health use of previously collected **research specimens** without consent when those specimens contain genetic information?
Q40	Under what conditions, if any, can researchers access previously collected **public health specimens** without consent when those specimens contain genetic information?
Q41	Should GINA be amended to permit employers to **access employees' genetic information** if it is relevant to protecting the health of others in the workplace?
Q42	Under what conditions, if any, should the law allow employers to use genetic information related to infectious disease in **hiring decisions**? Should employment contexts that involve exposure to high-risk infectious diseases be permitted to use host genetic information in hiring and placement of workers (e.g., workers in an Ebola biocontainment unit)?
Q43	Under what circumstances, if any, is it legally permissible for **health insurance, life insurance, disability benefits, and long-term care decisions** and rates to be based on genetic information related to infectious disease likelihood or severity?
Q44	If it is scientifically proven that a genetic variant predisposes people to a severe infectious disease response (e.g., long COVID), how might that affect **disability determinations under the Americans with Disabilities Act (ADA)**?

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probabilistically higher genetic risk for, say, infectious disease transmissibility.

Another social policy issue raised by blurring boundaries between disease categories are the tensions created among the areas of research, clinical practice, and public health practice as it becomes difficult for these areas of practice and policy to remain siloed. There are different justifications and policies for activities in the areas of research, clinical care, infection control, and public health operations, all of which could have activities related to genetics and infectious disease. *How do we manage these* ***conflicts*** *which are ongoing and likely to increase moving forward?* (see Q34 in Table 4). The silos around the different data sources in these areas are also crumbling, especially as it relates to the collection, storage, and use of genetic data, raising additional issues regarding privacy, data sovereignty, and other values, as genetic data flows across contexts.

Conclusion

Boundaries between infectious disease and genetic disease that many had perceived as clear and meaningful are becoming increasingly blurred. Host genomic factors are being sought to help explain infectious disease transmission, infection, and severity, and response to prophylaxis or treatment. The identification of such factors has implications for research, clinical management, public health practice, and policy.

During the COVID-19 pandemic, vaccination status and other risk factors have been used in decision-making regarding treatment access, death benefits, travel, and other aspects. It seems plausible that genetic risk information will be added to the calculus of such decisions in the future. Before this happens, it is critical to address the broad range of ELSI issues that would be raised by such a practice.

Broad expertise will be required to address these issues, including but not restricted to bioethics, genomics, history, infectious disease, law, philosophy, and public health. A similarly broad array of funding agencies should be interested in different aspects of this work.

Our intention is that working through the research agenda articulated here will help researchers, clinicians, policymakers and the public understand how the complexity of blurred boundaries came about, their implications, and how to manage the blurring in ways that do not recapitulate or exacerbate inequities at the intersection of genetic and infectious disease.

Notes

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