GENOMICS AND HIGH-CONSEQUENCE INFECTIOUS DISEASES: A SCOPING REVIEW OF EMERGING SCIENCE AND POTENTIAL ETHICAL ISSUES

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Host genomic research on high-consequence infectious diseases is a growing area, but the ethical, legal, and social implications of such findings related to potential applications of the research have not yet been identified. While there is a robust ethical debate about the ethical, legal, and social implications of research during an emergency, there has been less consideration of issues facing research conducted outside of the scope of emergency response. Addressing the implications of research at an early stage (anticipatory ethics) helps define the issue space, facilitates preparedness, and promotes ethically and socially responsible practices. To lay the groundwork for more comprehensive anticipatory ethics work, this article provides a preliminary assessment of the state of the field with a scoping review of host genomic research on a subset of high-consequence infectious diseases of relevance to high-level isolation units, focusing on its ethically relevant features and identifying several ethical, legal, and social implications raised by the literature. We discuss the challenges of genomic studies of low-frequency, high-risk events and applications of the science, including identifying targets to guide the development of new therapeutics, improving vaccine development, finding biomarkers to predict disease outcome, and guiding decisions about repurposing existing drugs and genetic screening. Some ethical, legal, and social implications identified in the literature included the rise of systems biology and paradigm shifts in medical countermeasure development; controversies over repurposing of existing drugs; genetic privacy and discrimination; and benefit-sharing and global inequity as part of the broader ecosystem surrounding high-level isolation units. Future anticipatory ethics work should forecast the science and its applications; identify a more comprehensive list of ethical, legal, and social implications; and facilitate evaluation by multiple stakeholders to inform the integration of ethical concerns into high-level isolation unit policy and practice.

Keywords: Bioethics, Genomics, High-consequence infectious diseases, High-level isolation units

A KEY POTENTIAL BENEFIT of research on the genomics of the host response to infectious diseases is the discovery of new targets for the development of therapies. A paradigm example is the CCR5 delta-32 allele, which confers resistance to HIV-1 in approximately 10% of in-

dividuals living in Europe and western Asia.¹ Its discovery launched research to develop therapeutics and vaccines targeting the CCR5 co-receptor.² Identifying pathways to new therapeutics, and other medical countermeasures like vaccines, is a central aim of a recent large-scale (8,000-

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person) case control study to identify host genetic factors underlying how the body responds to Ebola virus.³ This study will genotype people in Liberia who survived Ebola virus disease (EVD), had close contact with someone who had EVD, or have participated in an Ebola vaccine study.³ More than 17,000 people survived EVD,⁴ a large population enabling the rigorous investigation of multiple host genetic factors underlying innate immunity,⁵ disease risk, mortality, long-term sequelae, viral RNA persistence, humoral immunity, and Ebola vaccine response.³

It will be several years until the large-scale case control genetic study on EVD is complete. However, there is value in initiating an early conversation about the risks and benefits of such genomic studies, as well as the other ethical, legal, and social implications of future genetic findings about EVD and other high-consequence infectious diseases. While there is a robust ethical debate about the ethical, legal, and social implications of research during an emergency, there has been less consideration in the literature of issues facing research conducted outside of the scope of emergency response. Early consideration of such implications can help encourage ethically and socially responsible practices that consider individual and societal risks and benefits and promote justice.⁶ Increasingly, there are calls to bring ethical and social considerations into emerging science to steer applications in a socially responsible way, recommending interaction among science, technology, ethics, and social science to lay a foundation for the early recognition of emerging ethical, legal, and social implications and prospective policy responses.^{7,8}

In the United States, the National Ebola Training and Education Center (NETEC) and federal partners launched a consortium in 2016, the Special Pathogens Research Network (SPRN), to create critical national research infrastructure for special pathogens.⁹ The number of cases of a given disease admitted to high-level isolation units across the network will likely be low for genetic study, but the SPRN would be the key network for interfacing with international partners regarding global research collaborations and evaluation of the ethical, legal, and social implications raised by human subject research on high-consequence infectious diseases.

A complete analysis of the anticipatory ethics of emerging science and technology involves assessment, forecasting, ethical issue identification and evaluation, feedback of ethical concerns into study and technology design, and policy development.¹⁰ This article is a first step scoping review to assess host genetic research on a subset of high-consequence infectious diseases of relevance to high-level isolation units and potential ethical, legal, and social issues: EVD, Middle East respiratory syndrome (MERS), avian influenza (including separate searches for H5N1, H7N9, and H1N1), severe acute respiratory syndrome (SARS), Lassa fever, Marburg hemorrhagic fever (Marburg HF), monkeypox, smallpox, anthrax, and multidrug-resistant tuberculosis (MDR-TB). Highlighted in the review are the more ethically

relevant aspects of the science and ethical issues raised in the literature. The article concludes with recommendations for next steps in identifying, evaluating, and addressing potential issues raised by the discovery of host genetic information about high-consequence infectious diseases, especially as it relates to the care of patients in high-level isolation units.

METHODS

We decided that a scoping review was the method best suited to our goal of laying the groundwork for future anticipatory ethics analysis.¹¹ An exploratory, iterative approach was used to identify recent relevant scientific literature using Google Scholar. The lead author conducted multiple searches for articles published between 2008 and 2018 using the following keywords: “host genetic” OR “human genetic” AND high-consequence infectious diseases of potential interest: “Ebola,” “MERS,” “SARS,” “avian influenza” (with separate searches for “H5N1,” “H7N9,” and “H1N1”), “Lassa,” “smallpox,” “anthrax,” “Marburg,” “monkeypox,” and “MDR-TB.” To select this list, the authors were informed by ongoing NETEC discussions about pathogens that may activate a high-level isolation unit, but there is currently no consensus on a standardized list.

Since Google Scholar has lower precision and coverage than PubMed, it is not used for systematic reviews.¹² But for a scoping review aiming to rapidly identify a relevant body of articles, Google Scholar offered 2 advantages: its algorithmic relevance ranking and indexing of full text provided results that more readily disambiguated host/human genetic from pathogen genetic articles than in similar search strategies tested on PubMed.

In each search, the first 50 hits were scanned for potential inclusion in the review, with the goal of capturing a relevant subset of articles rather than complete capture. From these keyword searches, 88 articles were initially identified. After excluding less relevant and non-peer-reviewed articles, and using a snowball approach to find additional relevant citations,¹³ the total number of articles analyzed was 82. Article counts from each pathogen in order of greatest to least is as follows: avian influenza (31), Ebola (13), anthrax (12), SARS (8), MDR-TB (6), smallpox (6), Lassa (3), Marburg (1, but overlaps with Ebola), monkeypox (1), MERS (1). Not all articles in the sample are host genetic studies, but each at minimum posits that host genetics plays a role in shaping high-consequence infectious disease outcomes.

FINDINGS

Challenge of Low-Frequency, High-Risk Events

Overall, the science of the human genetics of high-consequence infectious diseases is at an early stage. For

pathogens of recent emergence, such as MERS-CoV, no human genetic studies have been published. Genome-wide association studies require large sample sizes to produce meaningful results about the genetic contribution to complex diseases, though outbreak investigations can be venues for hypothesis-generating studies of gene-environment interactions.¹⁴ For outbreak control, pathogen sequencing is emphasized because it yields more immediately useful information about transmission dynamics or virulence factors.

Susceptibility to infection is the result of complex interactions of environmental and genetic factors,¹⁵ and epidemiologic studies can point to instances where human genetic variability might contribute to infectious disease outcomes. Researchers have observed patterns in the epidemiology of H5N1 pointing to a potential role for host genetic susceptibility, due to familial clustering of cases, relative paucity of nonfamilial clusters, the occurrence of related cases distributed in location and time, and few cases in highly exposed groups.¹⁶ Without subsequent study and confirmation, such patterns only suggest potential host genetic contributions; it is difficult to separate genes from environment (eg, for H5N1, disentangling genetic and household exposure factors in familial clusters).¹⁷ In the sample of articles, avian influenza was the most widely studied infection, but a rigorous systematic review identified only 1 study providing good evidence for an important role for IFITM3 in susceptibility to severe influenza in mice, with some evidence linking IFITM3 to human A/H1N1/pdm2009 infection.¹⁸ The review emphasized that reliable knowledge will be produced only if multiple research groups form a consortium to generate enough cases for an adequately powered study, an issue broadly applicable to other high-consequence infectious diseases.

The rate of discovery may accelerate with emphasis on, and investments in, improving translation from bench to bedside, precision medicine, and the medical countermeasures pipeline. Over the past 10 years, a systems biology approach to host-pathogen interactions has taken off, using next-generation sequencing, gene expression profiling with proteomics and metabolomics, and global RNAi screens to identify host factors.¹⁹ Previously, translational difficulties have challenged mouse studies.²⁰ However, the Collaborative Cross (CC) mouse “panel,” which consists of 8 lines of recombinant inbred mice together serving as a next-generation platform for investigating the genetics of complex diseases, is attracting research interest for more closely approximating diverse outcomes in human disease, and host genetics of bacterial and viral infections has been a focal area for CC studies.^{21,22} Researchers hope CC findings will serve as a means to target and improve human genome-wide association studies by identifying promising candidate genes, biomarkers, and pathways for directed investigation; illuminating environmental factors and genetic subpopulations contributing to the variability observed in genome-wide association studies; and providing helpful information for evaluating therapeutic

strategies.²³ CC mouse models have been developed for 3 high-consequence pathogens—Ebola,¹² SARS, and H1N1²⁴—successfully producing a range of disease phenotypes reflecting important human aspects of disease.²⁵

Genetics may play a role in shaping a number of high-consequence infectious disease outcomes, influencing susceptibility (or resistance) to infection, disease progression and severity, immune responses, or response to preventive or therapeutic interventions.⁶ Whether a patient will develop chronic long-term sequelae (like post-Ebola syndrome)²⁶ or be at risk for persistent infection may also be influenced by genetics. In the sample of articles, virtually no evidence was cited for a genetic role in superspreading, except a single mouse study on influenza that identified a CC line that could model 1 kind of superspreading phenotype—an animal with high titers but little or no disease.²³

Applications

No forecasts of the field were identified by the scoping literature review, so it is difficult to comment on when applications of host genetic research on high-consequence infectious diseases will emerge. Over 40% of the articles (34/82) listed no applications. This makes sense, because in basic and descriptive research, authors are typically more conservative in making claims about applications. Our sample included a fair number of animal model studies (19.5%, 16/82) and nongenetic epidemiologic studies (7%, 6/82).

The most commonly cited application of host genetic findings was the identification of targets to guide the development of new therapeutics for high-consequence infectious diseases (32%, 26/82). In Ebola research, for example, targeting host processes and not just viral proteins in the development of therapeutics is an essential priority for the field.²⁵ A promising line of research for Ebola therapeutics was sparked by the discovery that the virus requires the Niemann-Pick Type C 1 protein (NPC1),²⁷ a cholesterol transporter, to enter human cells; biological samples from patients with Niemann-Pick disease (NPD), a rare genetic disorder often called “childhood Alzheimer’s,” revealed that this population is resistant to EVD, at least in the context of *in vitro* studies.²⁸

The second most commonly cited application of host genetic research was improving vaccine development (23%, 19/82), emphasized in the smallpox and anthrax articles. Large numbers of military personnel have been given smallpox and anthrax vaccines (administered mandatorily at different points in time), which has enabled the development of sizable longitudinal cohort studies studying vaccine response. Studies identified variations in adaptive immune response to the smallpox and anthrax vaccines associated with human leukocyte antigen (HLA) genes responsible for immune regulation,^{29,30} and investigated differences between different racial/ethnic groups. It will

take larger and more ethnically diverse studies to confirm a relationship between ancestral variation and vaccine response.³¹ One article framed differences in smallpox vaccine response as “genetic disparity” (estimating that 30% to 50% of the US population has contraindications to current versions) to argue for the importance of studying the biological basis of difference in immune response in the interest of developing better vaccines.²⁹ No studies suggested genetic screening for vaccine response as a potential application of the research, instead focusing on recommendations for rationalizing vaccine design.

The third most commonly cited application of host genetic research was using biomarkers to predict disease outcome (17%, 14/82). The most developed example came from articles on MDR-TB, where authors thought genetic markers predicting poor treatment response could flag patients for increased follow-up, and markers predicting rapid progression of TB (like *NRAMP1*) could be used for patient risk stratification.³² For the management of MDR-TB, these markers may hold more relevance for providers responsible for follow-up, and risk stratification may come more into play in a setting with multiple patients. Other articles mentioning biomarkers did so generally, citing prediction of outcome, early diagnosis, and understanding of disease course as benefits. The sample also included gene expression-based bioassays (cited in Lassa and anthrax studies)^{33,34} and kinetics of immune response (cited in an H7N9 study)³⁵ for monitoring and predicting disease progression and outcome.

The final 2 applications of host genetic information for high-consequence infectious diseases were cited infrequently in the sample: guiding decisions about repurposing existing drugs (5%, 4/82), and genetic screening or targeting of high-risk groups based on genetics (5%, 4/82). Repurposing existing drugs was cited in Ebola and Lassa articles. Like the biomarker articles, articles suggesting repurposing of existing drugs emphasized systems biology approaches for providing information that could guide application. One study developed a computational platform using Ebola proteomics data to identify and rank FDA-approved drugs, integrating information from *in vitro* studies to develop a final priority list of drugs for investigating efficacy using the Ebola CC mouse model.³⁶

Genetic screening was mentioned in studies of avian influenza and SARS. The avian influenza studies spoke generally of using genetic susceptibility information to help identify high-risk individuals or target them for prevention. A single SARS study envisioned a broader role for genetic screening.³⁷ This study, which genotyped 100 laboratory-confirmed SARS patients from the Chinese Han population in Taiwan, suggested that during a crisis, genetic screening could not only be helpful for identifying highly susceptible (high-risk) individuals for prevention efforts, but would also be useful for making staffing assignments, with the rationale that healthcare workers who were resistant to infection would be more suited to providing care.³⁸

Taiwan has genetic discrimination legislation, but many exceptions limit its scope, raising legal questions about whether genetic screening during an infectious disease crisis is permissible.³⁹

DISCUSSION

Analysis of the articles in the scoping review suggests that while genetic research will inform the development of therapeutics and vaccines to improve safety and efficacy, few applications will use genetics directly. The most likely direct use of genetics may be biomarkers to predict disease progression and outcome and inform patient care decisions, but only if confirmed and validated in subsequent research. If confirmed, genetic information about infectious disease may have practical and ethical relevance for various stakeholders. For high-level isolation units, if a patient is at increased genetic risk of becoming infected, this information is obviated by their illness, but for public health authorities, knowing who is at high risk prior to infection could be useful for targeted prevention measures.

In theory, high-level isolation units could make use of information about genetic susceptibility, resistance, and vaccine response to inform which providers are involved in direct patient care, but there are significant questions about whether such genetic screening should be performed. In the United States, the federal Genetic Information Non-discrimination Act (GINA) and some state genetic privacy laws prohibit employers from instituting mandatory genetic testing; employers may not use genetic information for employment status and health insurance, but they may offer employees confidential genetic testing as a voluntary health benefit.⁴⁰ However, it is unclear if the Public Health Service or Stafford Acts could be used to override GINA and state laws when the federal government declares a public health emergency.⁴¹ Furthermore, state public health emergency laws vary widely in content and in the powers they confer to override federal and state restrictions.⁴² Outside of the United States, many jurisdictions have no regulations governing genetic information. Clarifying US and international regulatory frameworks governing how genetic information can and should be used during a public health emergency is an area in need of work.

If using predictive biomarkers improves patient care, and benefits outweigh risks, the ethical questions raised are about how to integrate them responsibly and effectively. Genetic information predicting disease progression and severity could improve patient care and guide decision making about interventions. More ethically challenging is the use of this information for allocation of scarce resources. Whether high-level isolation units would make use of genetic information about patients' development of long-term sequelae is an open question; patients and providers responsible for long-term care would find this information useful.

A broader review of host factors in high-consequence infectious diseases would undoubtedly surface other kinds of bioassays relevant for understanding and predicting disease progression and outcome, given the increasing emphasis on systems biology. This underscores the importance of developing a broader framework for the ethics of using biomarkers that predict disease course and outcomes in high-level isolation units, when precision medicine will likely be driven by systems biology and integration of multiple data sources.⁸ The ethical, legal, and social implications of host genetics should not be considered separately from the other kinds of prognostic information used to make decisions about providing care in high-level isolation units.

Therapeutic targeting of the host immune response is another area of ethical, legal, and social concern; such an approach has seen success in the realms of cancer immunotherapy and autoimmune disease but has been attempted with less clear success in sepsis.³⁸ High-level isolation units may want to discuss how best to evaluate the risks and benefits of using host-directed therapies as they enter the medical countermeasures pipeline. For example, the unexpected discovery that cells from NPD patients are resistant to infection by filoviruses because they lack a protein Ebola virus uses to enter cells has defined a promising target (NPC1) for the development of Ebola therapeutics.⁴³ An ideal outcome from this line of research would be treatments effective for broad groups of Ebola patients, following in the footsteps of the creation of new antiretrovirals (CCR5-receptor agonists) for treating patients infected with CCR5-tropic HIV-1.⁴⁴ However, many bioethics, health and science policy, and public health experts have criticized precision medicine's pattern of producing expensive cures for a small number of people.⁴⁵ While high-level isolation units are in highly resourced settings with the potential to use precision medicine strategies, if host genetic research on high-consequence infections yields costly and narrowly applicable interventions, ethical questions about inequitable access and benefit will be raised.

Identification of targets through genomic and other -omic data not only facilitates new lines of research on therapeutics but is also used to screen existing FDA-approved drugs that may be repurposed for new uses.⁴⁶ Drug repurposing is often lauded as a potentially faster and cheaper avenue for new medical treatments, but pharmaceutical companies have little financial incentive to invest in trials to test new uses for off-patent drugs.⁴⁷ The repurposing potential of existing drugs remains unproven, raising concerns about unknown harms and the possibility of false-positive screens leading to ineffective use; just because a drug is safe and effective for one indication does not mean it will be so when used for a different disease.⁴⁸

None of the articles in the scoping review referenced a larger debate over the repurposing of existing drugs to treat Ebola. During the West African outbreak of 2014–2016, a

World Health Organization (WHO) panel decided that using experimental, unapproved drugs or vaccines was ethical under certain conditions, but researcher proposals to repurpose existing drugs like statins for treating host immune response raised controversy.⁴⁹ The scarcity of ZMapp raised questions about whether repurposing existing low-cost drugs should be considered, but since there was no safety and efficacy evaluation as treatments for EVD, many felt they were too risky for consideration. At stake in these questions were issues of global inequity and trust coloring public optics, where citizens from high-income countries were first in line for a scarce resource. Use of experimental therapies also raised the specter of historically exploitative drug trials in low-resource settings.⁵⁰

Issues of global inequity may not directly relate to the ethical questions providers in high-level isolation units will encounter on a daily basis, but they are an important aspect of the broader ecosystem surrounding high-level isolation units. If robust host genetic findings emerge from the Ebola survivor study that lead to the development of new therapies and vaccines, questions about equitable access in low-resource settings will likely emerge. There is precedent in the high-consequence pathogen space. During the H5N1 outbreaks in 2006, Indonesia stopped sharing virus samples with the WHO because it worried that pharmaceutical companies would make proprietary and unaffordable vaccines and therapies.⁵¹ Since then, a voluntary WHO benefit-sharing framework has been established for pandemic influenza to promote equitable access to vaccines and therapies, but no such global benefit-sharing framework for Ebola or other high-consequence pathogens has been developed.^{52,53} As a community that will benefit from the knowledge and applications derived from affected people and their participation in research, high-level isolation units could discuss how best to express support for the principles of benefit sharing and equitable access.

CONCLUSION

This scoping review outlined the state of the science of host genetics of high-consequence infectious diseases and identified several potential ethical, legal, and social issues arising from the literature. The science is at an early stage, but it is worth considering when and where in the translational pipeline high-level isolation units should start engaging with host genetic findings, applications, and their attendant ethical, legal, and social implications. The most frequently cited applications of host genetic research were the identification of targets for developing new therapeutics and the improvement of vaccine development. Less cited applications included the identification of biomarkers to predict disease outcome for improving patient care, use of genomic and other -omic data to screen existing drugs for repurposing, and genetic testing to identify high-risk individuals or to inform high-level isolation unit staffing decisions.

From an ethical, legal, and social implications perspective, both new and repurposed drugs raise questions about safety and efficacy, as well as economic considerations that affect access. New drugs are likely to be expensive, as other examples from precision medicine illustrate, and may not be applicable to broader populations. Repurposed drugs may offer cheaper alternatives, but their benefits and risks will remain unproven without policy changes to incentivize trials. While genetic discrimination laws, especially in the United States, make genetic testing of healthcare workers an unlikely application, not all jurisdictions have the same restrictions. Furthermore, given an increasing emphasis on systems biology, high-level isolation units will need to consider the broader ethics of using biomarkers that predict disease course and outcomes in patient care, since host genetic markers are only one of many potential biomarkers that may be discovered.

Our assessment does not represent a comprehensive anticipatory ethics analysis. There is a need to more thoroughly forecast the future of the science and its applications, identify and evaluate ethical issues, and encourage dialogue between multiple stakeholders to inform the integration of ethical concerns about host genetic research and its applications for high-level isolation unit policy and practice.

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