Roles of genetics and blood type in clinical responses to COVID-19: ethical and policy concerns

Robert Klitzman

Psychiatry, Columbia University, New York City, New York, USA

Correspondence to
Dr Robert Klitzman, Psychiatry, Columbia University, New York City, NY 10032, USA; rlk2@columbia.edu

Received 22 September 2020
Revised 11 November 2020
Accepted 16 November 2020
Published Online First 9 December 2020

ABSTRACT

Recently, several genetic variants have been associated with increased or decreased risks of becoming infected and/or seriously ill with COVID-19—not only offering important potential medical benefits but also posing critical ethical questions. These genetic factors, some of which are associated with blood type, may account for variations in observed responses to COVID-19. Hence, assessments of these genetic differences and blood type could provide possible benefits in gauging patients' risks of disease acquisition and prioritising allocation of interventions or vaccines, if supplies are limited. The media has widely reported these findings, and people online are now discussing their blood type and its possible effects on their COVID-19 risks, but several ethical concerns arise. Individuals possessing genetic variants or blood types associated with lower risk may engage in 'risk compensation', erroneously assuming that they can protect themselves less, and hence less frequently wearing masks or washing hands. Given the ongoing COVID-19 pandemic, many physicians, hospitals, patients, policymakers, members of the public, testing companies and others may well consider these factors in making critical prevention/treatment decisions. Researchers, providers and others should thus begin to address these concerns. Increased awareness and education aimed at providers, patients, family members, public health officials, political leaders and the public-at-large are critical. Attitudinal research is vital to examine how providers, patients and the public understand these findings. Ethical frameworks and guidelines are needed, addressing whether such genetic information should be incorporated into decisions regarding allocation of scarce resources—including hospital and ICU beds, ventilators, medications (eg, remdesivir) and vaccines—and if so, how.

Recently, several genetic variants have been associated with increased or decreased risks becoming infected with COVID-19 or seriously ill, if infected[1]—not only offering important potential medical benefits but also posing several critical questions. Investigators see potential 'usefulness' of testing for these genetic factors in 'clinical risk profiling of patients'.[1] Especially since limited resources for COVID-19 prevention and treatment will likely continue, additional types of testing and assessment can potentially help in making difficult prevention and treatment decisions.

GENETIC DIFFERENCES ASSOCIATED WITH PHYSIOLOGICAL RESPONSES TO COVID-19

Ellinghaus *et al*[1] found associations between severe COVID-19 disease, defined as respiratory failure, and several genetic markers, including those associated with blood type. A group of six genes on chromosome 3 heightened risks of respiratory failure by 56%[1] and are found in about 5% of Europeans, 30% of South Asians and 63% of Bangladeshis.[2] Genes on chromosome 9 associated with blood type O decrease risks of infection by around 20%–35%, and those associated with type B and Rh factor positivity increases the risks by around 10%–28%.[3–6] Rare genetic variants have also been associated with immunological defects in response to COVID-19.[7] In the near future, researchers may very well identify additional such genetic markers as well.

While these studies have shown relationships between blood types and risks of becoming *infected* with COVID-19, the relationships between blood type and risk of intubation and death are less clear. Though Latz found that blood type was associated with infection, but not with intubation or death,[6] Ellinghaus *et al*[1] found that blood type was associated with respiratory failure, and blood type has been associated with death[8] and hospitalisation.[9] Rates of intubation, however, may vary based on the practice of individual hospitals and countries, development of improved interventions and advances in treatment over time.

Genetic and serological testing and information could thus potentially provide possible benefits, helping to gauge patients' risks of disease acquisition or needs for more aggressive initial treatment. These genetic factors could also affect individuals' differential responses to vaccines and medications—for example, why a vaccine or treatment is effective in only, for instance, 50% of individuals, and/or why a vaccine leads to development of antibodies or long-term or short-term immunity in only certain subsets of individuals. Such findings could thus prompt suggestions that individuals whose genetics indicate that they will respond favourably should receive priority in receiving these interventions, if supplies are limited.

Yet ethical concerns emerge, posing challenges for physicians, researchers, patients and the public. The media has widely reported these research findings and, anecdotally, many people online and elsewhere are now discussing their blood type and wondering whether it might affect their odds of becoming infected or seriously ill, with some individuals feeling relieved they have blood type O. As Latz said, 'I've had a lot of physicians who are using our paper to tell patients not to be overly worried' if they lack type O.[10] Though Latz has thus expressed concern about overzealous interpretation of some of these research findings,[10] these concerns and these implications have not heretofore examined.

To cite: Klitzman R. *J Med Ethics* 2021;**47**:149–151.

23andMe has been asking consumers to participate in research to identify genetic variants associated with COVID-19 infection and outcomes[11] and has reported data indicating that blood type and genetic variation are associated with infection and hospitalisation.[9] The company advertises that a benefit of participating in this research will be to 'have the option to learn more about yourself through genetics'.[11] Whether the company will provide results now or in the future to consumers who enter the study or seek genetic testing through the company more broadly is not yet clear. Given the newness of both COVID-19 and these genetic discoveries, and the fact that scientific understandings about them are still evolving, companies that do not yet offer such testing will very likely consider doing so in the near future. Given that such companies are already engaging in research, they could potentially provide such tests and results to consumers as part of research studies that would not necessarily require US Federal Food and Drug Administration approval. Commercial labs could easily begin genetic testing related to COVID-19 responses. Direct-to-consumer and other genetic testing companies already offer a wide range of genetic tests, even in the absence of clinical utility or any FDA-approved uses (eg, purporting to predict risks of opiate addiction).[12]

Over the upcoming months, desperate to combat the ever-rising COVID-19 pandemic, many physicians, patients, policymakers, members of the public, testing companies and others may thus well consider genetics and blood types in making critical COVID-19 prevention and treatment decisions.

ETHICAL AND OTHER CONCERNS

Yet use of genetic and blood type information in discussions about COVID-19 poses several critical ethical concerns. Individuals possessing genetics or blood types associated with lower risk may erroneously assume that they can protect themselves less, and hence less frequently wear masks or wash their hands after possible exposures. Conversely, individuals who learn they possess risk-increasing genetics or blood types might consequently safeguard themselves more carefully and also face added stresses and anxiety. Researchers have described 'risk compensation', in which people engage in riskier behaviours if they have acted in ways that they feel are protective.[13] Seat belt use, for example, has failed to reduce fatal car accidents, since drivers wearing seat belts then compensate and drive faster or less cautiously.[14] Sunscreen use has raised rates of melanoma, since people who apply sunscreen feel that they are now safe to expose themselves to more sun.[15] Gay and bisexual men who take pre-exposure prophylaxis to prevent HIV subsequently use condoms less, feeling they are 'safe', but increasing their rates of chlamydia by 59%, and of any sexually transmitted infections by 46%.[16]

Family members, employers or others could also potentially use these factors to encourage or pressure certain individuals who have 'protective genes' or blood types to return to work sooner and/or put themselves at heightened risk. Risk compensation could affect bystanders, too, since lower risk individuals who engage in risk compensation and thus forgo masks can still be infectious, leading to asymptomatic spread. On the other hand, if subsequent genetic research found that lower risk individuals were actually not infectious, society could potentially rely on them more for inperson jobs and to protect more vulnerable individuals

Crucial social justice concerns surface, too, since distribution of these genes and blood types also differ significantly by race and ethnicity. In the USA, blood type A, for instance, is found among 38% of Caucasians, but only 25.2% of African Americans.[17] Efforts to incorporate such genes in allocation decisions thus need to ensure that these factors are not used in ways that exacerbate existing social inequities.

Moreover, many key aspects of the roles of these genetic factors remain unknown. Additional variables (eg, age, premorbid conditions, gender, race, ethnicity and social determinants of health/exposure, including healthcare access and workplace and living arrangements) may also affect risks of infection and symptoms. These genetic and serological studies may thus have several potential limitations, since they vary in how much they include these other variables as well as treatment administered and other details of patients' clinical courses. Nonetheless, consensus appears to be emerging that COVID-19 infection is independently associated with certain blood groups. Investigations are needed, however, to further elaborate on certain other associations reported thus far.

MOVING FORWARD: ADDRESSING CHANGE

The critical ethical concerns presented here need to be addressed in several ways. Further research among diverse global populations is essential to investigate precisely how protective these genetic and serological differences may be, especially among patients of different ages, ethnicities and prior diagnoses, and how physicians, patients and families may interpret or misinterpret these factors or integrate them into treatment or prevention decisions. The paucity of data on the prevalence of several of these genetic markers in other populations, in particular, is striking and needs to be rectified. Attitudinal and behavioural research is also vital, to examine systematically how providers, patients and the public understand and interpret these findings—whether they feel that genetic or blood type information is, or may be, helpful, and if so, how and when, or whether such information may affect their COVID-19 prevention or treatment decisions, and if so, how, and what factors (eg, socioeconomic status, age, race/ethnicity, education, prior disease experience, and knowledge of COVID-19, and of patients who have recovered or died) may affect these perceptions.

Educational efforts addressing these challenges are critical, earlier rather than later, aimed at providers, patients, family members, public health officials, political leaders and the public-at-large, including appropriate public health messaging.

Professional associations, bioethicists and others should consider developing ethical frameworks and guidelines regarding use of these genetic and serologic factors—whether the presence or absence of such genes or blood type should be incorporated into decisions, and if so, how, and what possible advantages and disadvantages may exist—for example, regarding triage and allocation of scarce resources, including giving lower or higher priority to certain patients in deciding admissions to hospitals and/or ICUs, use of ventilators, medications (eg, remdesivir) or vaccines, if only limited supplies of these interventions are available—as has often, and will likely continue to be, the case.

Frameworks for allocation of scarce resources in treating COVID-19 have been proposed, mostly taking into account Sequential Organ Failure Assessments and emphasising processes of transparency and inclusions,[18 19] age and comorbidities. However, these proposals have not yet incorporated genetic or blood type information, which differ in several ways from the other factors heretofore considered. Published reports to date have tended to examine relationships between COVID-19 patients clinical outcomes among and other, more apparent and routinely obtained comorbidity and sociodemographic, rather

than blood type and genotypic information. Genotypic information also indicates that certain individuals are at decreased, not just increased risk of COVID-19 acquisition and symptom severity. While comorbidities divide the population into two broad categories of increased risk or not, genotypes segregate the population as a whole into three groups—those at decreased, increased or unaltered risk.

Knowledge of genetics and types could potentially be used in allocation of scarce resources in several ways. For instance, individuals who, based on their genetics or blood type, would gain the most from an intervention may go from very low to very high prioritisation. Individuals who are most likely to have a good clinical outcome, even if they are not very badly off without the intervention, may also increase to higher prioritisation, though not as much. Those who would be worst off in the absence of the intervention, but less likely to benefit, based on their genetics, may increase, but still have relatively low prioritisation.

Frameworks or guidelines concerning genetic and serological information should seek to promote both procedural and distributive justice, aiming for fair processes, with inclusion of all relevant stakeholders, including experts in public health, genetics, and COVID-19 prevention and treatment, ethicists and representatives of ethnic and racial groups and disability communities that are at heightened risk of COVID-19 infection and symptoms.

CONCLUSIONS

The identification of genetic variations and blood types associated with physiological responses to COVID-19 can potentially provide important medical and public health benefits,especially given widespread desperation about the growing global pandemic, but also raises critical ethical questions and challenges that need to be addressed through appropriate education, research guidelines and practice. Given the ever-rising global pandemic, with its uncertainties due to the newness of the virus, and the widespread desire to respond as much as possible, we urgently need to consider and prepare to address these issues.

Twitter Robert Klitzman @RobertKlitzman

Acknowledgements The author thanks Lundyn Davis, Jiseop Kim and especially Patricia Contino for their assistance in the completion of this manuscript.

Funding Funding for this research provided by the National Human Genome Research Institute (# 5RM1HG007257-08).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Robert Klitzman http://orcid.org/0000-0002-6827-8063

REFERENCES

1 Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, *et al*. Genomewide association study of severe COVID-19 with respiratory failure. *N Engl J Med* 2020;383(16):1522–34.
2 Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neandertals. *BioRxiv* 2020 https://www.biorxiv.org/content/
3 Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. *medRxiv* 2020. doi:10.1101/2020.04.08.20058073. [Epub ahead of print: 11 Apr 2020].
4 Zhao J, Yang Y, Huang H, *et al*. Relationship between the ABO blood group and the COVID-19 susceptibility. *medRxiv* 2020.
5 Wu Y, Feng Z, Li P, *et al*. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. *Clin Chim Acta* 2020;509:220–3.
6 Latz CA, DeCarlo C, Boitano L, *et al*. Blood type and outcomes in patients with COVID-19. *Ann Hematol* 2020;99(9):2113–8.
7 van der Made CI, Simons A, Schuurs-Hoeijmakers J, *et al*. Presence of genetic variants among young men with severe COVID-19. *JAMA* 2020;324(7):663–11.
8 Padhi S, Suvankar S, Dash D, *et al*. ABO blood group system is associated with COVID-19 mortality: an epidemiological investigation in the Indian population. *Transfus Clin Biol* 2020;27(4):253–8.
9 Yamamoto FJosep Carreras Leukaemia Research Institute2020ABO blood groups and SARS-CoV-2/COVID-19 infection (version 3)
10 Rubin R. Investigating whether blood type is linked to COVID-19 risk. *JAMA* 2020;324(13).
11 23andme. Your DNA could contribute to COVID-19 research: join the 23andme COVID-19 study. Available: https://you.23andme.com/covid19-study/ [Accessed 3 Nov 2020].
12 Klitzman R. The need for vigilance in the marketing of genomic tests in psychiatry. *J Nerv Ment Dis* 2015;203(10):809–10.
13 Cassell MM, Halperin DT, Shelton JD, *et al*. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006;332(7541):605–7.
14 Richens J, Imrie J, Copas A. Condoms and seat belts: the parallels and the lessons. *Lancet* 2000;355(9201):400–3.
15 Vainio H, Bianchini F. Cancer-Preventive effects of sunscreens are uncertain. *Scand J Work Environ Health* 2000;26(6):529–31.
16 Traeger MW, Schroeder SE, Wright EJ, *et al*. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. *Clin Infect Dis* 2018;67(5):676–86.
17 Fang C, Cohen HW, Billett HH. Race, ABO blood type and VTE risk: not black and white. *Transfusion* 2013;53(1):187–92.
18 White DB, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. *JAMA* 2020;323(18):1773–4.
19 Maves RC, Downar J, Dichter JR, *et al*. Triage of scarce critical care resources in COVID-19 an implementation guide for regional allocation: an expert panel report of the task force for mass critical care and the American College of chest physicians. *Chest* 2020;158(1):212–25.