The First Baby Born After Polygenic Embryo Screening: Key Issues Through the Lens of Experts and Science Reporters

Kalina Kamenova, Hazar Haidar*

ABSTRACT

This article examines the bioethical discourse on polygenic embryo screening (PES) in reproductive medicine in blogs and news stories published during 2021 in response to the first baby's birth using polygenic risk scores (PRS) derived from genome-wide association studies. We further contextualize the findings by synthesizing the emerging peer-reviewed bioethics literature on the issue, which has emphasized considerations regarding the child-parent future relationship, equity of access, and the absence of professional guidelines. Our media content analysis has established that expert opinion was prominently featured in news coverage, with bioethicists and other academics contributing 38 percent of articles and providing extensive commentary on ethical, social, and policy implications in the articles written by journalists. The overall perspective towards the use of PES was primarily negative (59 percent of the articles), without significant differences in negativity and positivity between experts and science reporters. This indicates a shift from the predominantly neutral attitudes towards the technology in media discourse prior to its deployment in clinical settings. There is heightened awareness that offering these tests to prospective parents is unethical and can create unrealistic expectations, with the two most prominent arguments being uncertainty about the prediction accuracy of polygenic risk scores in this context (72 percent of the articles) and the potential of PES to lead to a eugenic future of human reproduction that normalizes the discrimination of people based on their genetics (59 percent of the articles).

Keywords: Polygenetic Embryo Screening, Reproductive Ethics, Unified Patient Lobby, Patient Autonomy

INTRODUCTION

The possibility of using genetic technologies to engineer the perfect baby has long haunted the public imagination. While some techno-utopians have openly advocated for human genetic enhancement, many critics have warned that advances in DNA technology come with myriads of ethical dilemmas and

* Kalina Kamenova, PhD, Research Director, Canadian Institute for Genomics and Society
Hazar Haidar, PhD, Assistant Professor, Université du Québec à Rimouski (UQAR)

© 2021 Kamenova & Haidar. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction, provided the original author and source are credited.
potentially dangerous social consequences. Literary and cinematic works have offered dystopian visions of our genetic futures—from Aldous Huxley’s powerful socio-political fantasy in his book *Brave New World* (1932) to cult classics of sci-fi cinema, such as *Blade Runner* (1982) and *Gattaca* (1997), there has been no shortage of ominous predictions that genetic engineering would lead to a new form of eugenics, which would ultimately create new social hierarchies grounded on genetic discrimination. Moreover, concerns about the use of genetic and genomic technologies for social control have been entangled with deep philosophical questions about personal autonomy, the right of the child to an open future, and the morality of changing, improving, or redesigning human nature.¹

The perennial debate on human enhancement was recently reignited with a new controversy over the use of pre-implantation screening of embryos using polygenic risk scores.² While the profiling of IVF embryos to detect hereditary, monogenetic diseases has been widely accepted, some companies are now pushing the envelope with unrealistic promises of tests that can predict genetic possibilities for desirable traits such as a child’s intelligence, athletic ability, and physical appearance. One event that prompted a public outcry in late 2021 was news about the birth of the first baby from an embryo selected through polygenic testing, a girl named Aurea.³ Although the embryo screening in Aurea’s case was used to decrease the likelihood for certain health conditions, many commentators believed that it signaled a real possibility of embryo selection for non-medical reasons becoming a commercial procedure in the foreseeable future, especially in the largely unregulated US fertility market.⁴

In the past, there have been discrepancies in how ethical and policy issues arising from advances in reproductive medicine have been viewed by experts (e.g., bioethicists, philosophers, legal scholars) and presented in the news. Like other advances in medical genetics, gene editing and screening technologies have been frequently characterized by exaggeration, sensationalism, and hype around clinical possibilities.⁵ Moreover, news media have often amplified the anticipated health benefits of genetic testing while overlooking uncertainty associated with its clinical validity and emerging ethical concerns, as shown in a recent study of the media portrayal of non-invasive prenatal testing (NIPT).⁶ The issue of polygenic embryo screening (PES) initially gained traction in the media in 2017 when the New Jersey biotech startup Genomic Prediction made headlines with claims that its testing technology could identify and avoid implanting embryos with very low IQs.⁷ The company also claimed that it had the capability to identify embryos with high IQs, although it committed not to offer that procedure for ethical reasons.⁸

The media coverage of polygenic risk scoring of human embryos between 2017 and 2019 was previously analyzed in a study published in *BMC Medical Ethics* in September 2021.⁹ This media content analysis has established that while most news articles were neutral towards the technology, one of the most significant critiques raised by science reporters was the absence of solid scientific evidence for the technology’s predictive accuracy and its practical value in IVF settings. It has also identified five major ethical concerns articulated by science reporters that have also been addressed in the academic discourse and within broader policy debates on reproductive technologies: a slippery slope towards designer babies, well-being of the child and parents, impact on society, deliberate choice, and societal readiness.

In this article, we examine the discourse on PES in bioethics blogs, opinion articles, and news stories published in 2021, with a specific focus on reactions to the birth of the first polygenic risk score baby. We compare the perspectives of experts and science reporters to establish their attitudes towards PES, the main ethical themes in press coverage, and the key issues highlighted for a future policy debate. We also juxtapose our findings to the previous study of media coverage to establish if the case of baby Aurea has raised any new issues and pressing ethical concerns.
I. Polygenic Embryo Screening in Reproductive Medicine

While complex diseases and human traits result from a combination of genetic, lifestyle, and environmental factors, genomic medicine is quickly gaining momentum, and demands for genetic tests in clinical practice have significantly increased. Scans and analyses of genomes from various populations, a research area known as genome-wide association studies, have enabled scientists and researchers to identify genetic differences or variants associated with a particular trait or medical condition. These variants can be combined into a polygenic risk score that predicts an individual’s traits or increased risk for a certain disease. For instance, PES have been used to predict a range of diverse common conditions, from diabetes and cancer to attention deficit issues and, in some cases, well-being in general. This testing modality relies on the probabilistic susceptibility of individuals to certain diseases to offer personalized medical treatments and inform therapeutic interventions.

Polygenic embryo screening uses polygenic risk scores to assess an embryo’s statistical risks of developing diseases (e.g., cardiovascular diseases) and potentially traits (e.g., intelligence, athletic ability, among others) and is performed in an IVF setting. It is currently marketed by several US companies such as MyOme, OrchidHealth, and Genomic Prediction to prospective parents as a method to screen pre-implantation embryos for health and non-health related conditions and is accessible to those who can afford to pay for it. As stated in a recent report on companies bringing PES into reproductive medicine, Genomic Prediction has already made their test for polygenic disorders, LifeView, available to couples. In contrast, Orchid Health has only recently invited couples to an early-access program for their testing technology, and MyOme is still in the process of launching its own test.

In September 2021, Bloomberg first reported the birth of baby Aurea using screening conducted by Genomic Prediction. She was born after her parents used IVF and subsequently PES to select from 33 candidate pre-implantation embryos in 2020. Aurea’s embryo was deemed to have the best genetic odds of avoiding conditions such as breast cancer, diabetes, heart disease, and schizophrenia in adulthood. It is worth noting that Genomic Prediction made the announcement almost one year following Aurea’s birth, thus delaying the media’s reaction to this development and the ensuing bioethical and policy debates.

II. Ethical, Social, and Policy Implications

Some important ethical, social, and regulatory considerations regarding the development and clinical use of PES have been raised within the academic community. The bioethics literature on the issue, however, appears rather thin, which is not surprising given that prior to 2021, the possibility of using this screening method in clinical practice was largely hypothetical. Other genomic technologies that have enabled polygenic embryo selection, such as whole-genome sequencing and pre-implantation genetic diagnosis, have received more attention from bioethicists, legal scholars, and Ethical, Legal, and Social Implications (ELSI) researchers. Our analysis of the emerging literature has shown that some proponents of PES advocate its current use and go as far as to suggest a permissive regulatory environment for the purpose of outpacing the ethical concerns and potential restrictions once the technology becomes widely available. This approach suggests that embryo selection should be allowed for or against any trait associated with higher odds for better health and well-being in general, often without further discussion of what accounts for well-being. Scholars applying the principle of procreative beneficence to defend the use of PES have also argued for regulation that addresses issues of justice and equality and expands access to the procedure for those who are currently unable to afford it. By contrast, opponents have argued that the clinical utility of this embryo selection method is yet to be proven, and its current use may create unrealistic expectations in parents, making it an unethical practice to offer the procedure as part of IVF treatments. They state
that predictive models from PRS have been developed with data from genomes of adult populations. Therefore, extrapolating results for embryo screening, along with the absence of a research protocol to validate its diagnostic effectiveness, is dangerous and misleading. Another layer of complexity is added because PRS already faces many translational hurdles that would undermine its predictive value assessment for certain traits or diseases. Scientists have noted that PRS take into consideration the genetic component of a particular trait putting aside the effects of other non-genetic factors, such as lifestyle and environment, which might interfere and influence the calculation of these scores.

Discussions on the ethics and societal implications of PES in the bioethics literature can be grouped into three distinct categories: 1) relational issues between parents and the future child (e.g., selection as identity-determining, concerns about the instrumentalization of children and the child’s right to an open future); 2) concerns about social justice and equality (e.g., fears about a new eugenics that establishes new social hierarchy, limited access to the technology due to its cost); and 3) implementation and regulatory concerns (e.g., lack of professional guidelines and advertising of PES by private companies). An important ethical implication of PES relates to the well-being of the future child and the way that selecting children based on their genetic make-up might negatively affect the parent-child relationship. This is in line with previously raised ethical concerns in the literature around cloning and pre-implantation genetic diagnosis that by choosing a child’s genetic predisposition, we are limiting to and, in some cases, denying their right to an open future. For instance, the future child’s options would be restricted if parents chose a genetic predisposition to musicality that might interfere with the child’s ability to make certain life choices.

On a societal level, there are concerns PES may alter social perceptions of what is “normal” and “healthy,” resulting in discrimination and stigmatization of certain conditions. Related to this are fears about encouraging eugenic attitudes that can exacerbate discrimination against people with disabilities.

Furthermore, one of the main ethical concerns raised is that the growing use of PES might exacerbate societal pressure to use this technology, influencing parents’ decisions to select the embryo with the “best” genetics giving rise to a generation of “designer babies.” Finally, direct-to-consumer marketing and clinical introduction of the technology prior to the publication of professional guidelines and in the absence of scientific validity for its use, as well as without appropriate regulatory oversight, is seen as a premature step that might erode public trust.

III. News Stories and Expert Commentary on Polygenic Embryo Screening in 2021

We conducted searches on google news using keywords such as “polygenic embryo screening,” “polygenic risk scores,” “baby Aurea,” and “embryo selection” and selected blogs and articles from major news sources (e.g., Washington Post, New York Times, Wall Street Journal, LA Times, Guardian, The Times, etc.). An additional effort was made to collect all relevant articles from prominent bioethics blogs such as the Hastings Center Bioethics Forum, Impact Ethics, Bioethics.net, Biopolitical Times (Center for Genetics and Society), among others. The time period for the study was one year, from January 1 to December 31, 2021. While most coverage occurred after the Bloomberg report on the birth of the first baby using PES, there were a number of news stories and blogs in response to a special report on embryo selection based on polygenic risk scores published in the New England Journal of Medicine on July 1, 2020. This report, which has received significant attention in the press, warns that companies that offer genetic services can create unrealistic expectations in health providers and prospective parents through their marketing practices. It has further emphasized the scientific uncertainty around the predictive results of PRS in the context of embryo selection. In general, our search has established that the news media coverage on PES over the past year has revolved around these two events – the NEJM Report and the announcement about the first
baby born after PES. In total, we collected 29 publications, of which 12 were blog posts and 17 publications under the general category of “news,” including ten news articles, three opinion pieces/perspective articles, two press releases, and one radio broadcast transcript (see Supplementary Material).

IV. Methods for content analysis

We utilized an inductive-deductive process to develop coding categories for a systematic content analysis of the blogs and new articles. The first author undertook a close reading of the entire dataset to derive inductively recurrent themes and ethical arguments in the media representations of PES. Based on this preliminary analysis, both authors agreed on the categories for textual analysis. The coding book was further refined by using a deductive approach that incorporates themes that have been previously articulated in the scholarly literature on the issue, particularly questions about the perceived attributes of the test, ethical concerns, and emerging policy considerations. The following categories were used to analyze key issues and attitudes towards PES expressed by experts and science journalists:

a. Claims that PES is unethical because it violates the future child’s autonomy.

b. Concerns about PES as a step towards eugenics and/or genetic discrimination.

c. Defenses of PES with arguments that parents have a duty to give the child the healthiest possible start in life (and reduce public health burden).

d. Claims that the science behind PRS-based diagnostics is uncertain, and it will take some time to prove its clinical validity.

e. Concerns about the equality of access to PES.

f. Arguments that PES can exacerbate ethnic and racial inequality (e.g., that most polygenic scores are created using DNA samples from individuals of European ancestries and predictions may not be accurate in other populations).

g. Arguments that PES provides health benefits and can help overcome genetic and health inequalities.

h. Concerns about the negative impact that PES may have on the child-parent relationship.

i. Arguments about the need for better regulatory oversight of PES.

j. Suggestions that there is an urgent need for deliberation and debate on the societal and ethical implications of PES.

k. Concerns that patients and clinicians may get the impression that the procedure is more effective and less risky than it is.

l. Assessment of whether the article’s perspective towards the use of PES is positive, negative, or neutral.

We used yes/no questions to detect the frequencies of mentions in each category, except on the last question, which required a more nuanced, qualitative assessment of the overall tone of the articles. We coded articles as “positive” when the authors viewed the technology favorably and emphasized its potential health benefits over its negative implications. Articles that did not condone the current use of PES and expressed strong concerns about the predictive accuracy of this testing method, its readiness for clinical use, and highlighted its controversial ethical and social implications were coded as “negative.” Finally, articles that simply presented information about the topic and quoted experts on the advantages and disadvantages of using PRS for embryo selection without taking a side or expressing value judgments were coded as “neutral.” Acknowledging the complex polysemic nature of media texts, we took into consideration that support or disapproval of PES may be implicit and expressed by giving credence to some experts’ opinions over others. Therefore, we coded articles that mostly cited expert opinion favorable to
PES, or alternatively, presented such views as more credible, as “positive”, while we coded articles that emphasized critical perspectives as “negative.”

V. Media Discourse and Expert Opinion On PES

We found out that perspectives and opinions by experts were prominently featured in both news (17 articles) and blogs (12 articles). The blog posts in our dataset were written by university professors in bioethics (four articles), academics from other disciplines such as medicine, political science, psychology, human genetics, and neurobiology (four articles), and science journalists and editors (four articles). Furthermore, three of the news articles in influential newspapers and magazines such as The Wall Street Journal, The Washington Post, and The Scientific American were opinion articles or commentaries contributed by academics (e.g., a psychology professor, specializing in personality, individual differences, and behavior genetics, a sociology professor, and a director of research in a graduate program in human genetics). The remaining 14 news articles in our dataset were written by science reporters, editors, or other staff writers. Altogether, experts contributed 38 percent of the media coverage (11 articles) on the issue of PES and its wider societal implications.

Experts’ comments were also heavily featured in the 18 articles written by science reporters and other media professionals, which accounted for 68 percent of the dataset. Of these articles, 17 extensively cited experts with academic and research backgrounds (professors and research scientists), seven articles quoted industry representatives (e.g., CEOs and spokespersons of Genomic Prediction and Orchid, other commercial developers), and four articles included opinions by parents seeking PES, particularly Aurea’s father, North Carolina neurologist Rafal Smigrodzki, who argued that a parent’s duty is to prevent disease in their child.23

The overall perspective towards the use of PES was mostly negative – 59 percent (17 articles) expressed negative attitudes, while 24 percent (seven articles) were positive and 17% (five articles) were neutral in tone and did not advance arguments in favor or against the technology and its adoption. However, we did not establish significant differences in negativity and positivity between experts and science reporters. For instance, 49 percent of the articles with negative attitudes were written by experts, while 53 percent were authored by science reports. Similarly, the articles by experts with positive perspectives on PES accounted for 13 percent of the dataset, while science reporters contributed 11 percent of the positive articles.

VI. Major Themes and Issues

The most discussed issue in media coverage was the prediction accuracy of polygenic risk scores and the uncertainties regarding the utility of these tests in embryo screening. Our analysis has established that 72 percent of the articles (21 out of 29) argued that the science behind PES-based diagnostics is uncertain, and it will take some time to prove its clinical validity. The second most frequently mentioned issue was the potential of PES to lead to a eugenic future of human reproduction. More than half of the articles (59 percent or 17 out of 29) raised concerns that PES could become a step towards a new form of eugenics that could eventually normalize the discrimination of people based on their genetics.

Despite concerns about the accuracy of PES testing, many articles gave extensive attention to problems concerning equality of access to PES and related diagnostic services, with 49 percent of the articles (13 out of 29) expressing concerns that the procedure is currently offered at a high cost, it is not covered by health insurance plans, and people of lower socioeconomic status cannot afford it. Furthermore, 41 percent of the articles (12 out of 29) raise concern that the current use of PES reflects the existing ethnic and racial
inequalities since most PES are created using DNA samples from individuals of European ancestries, and predictions may not be accurate in other populations. Although it has been reported that Genomic Prediction considers offering the procedure to parents of non-European ancestries, their messaging has suggested it would take a significant time to provide them with predictive models that are as relevant as those for European populations.\textsuperscript{24}

The health benefits of this testing technology, its regulation, and the need for a wider debate on how to realize its promise in a responsible manner were also addressed, albeit to a lesser extent. The potential to overcome genetic and health inequalities by selecting healthy embryos with the best odds against diseases and chronic conditions was emphasized in 41 percent of the articles (12 out of 29). The regulation was a topic covered in 38 percent of the articles (11 out of 29), in which the authors argued that better regulatory oversight of PES is needed, especially in the present condition of an unregulated US market for genetic testing. Additionally, 38 percent suggested that there is an urgent need for deliberation and public debate on the societal and ethical implications of PES. Finally, the issue that patients and clinicians may get the wrong impression that the procedure is more effective and less risky was addressed in 31 percent (nine out of 29).

We have established that critical issues about how PES may affect the well-being of the future child and the child-parent relationship have received less attention. For instance, only 17 percent of the articles (five out of 29) supported the clinical use of PES with arguments that parents have a moral obligation to give the child the healthiest possible start in life, a line of thought that is prominent in the bioethics literature on procreative beneficence and procreative autonomy.\textsuperscript{25} These authors also maintained that the technology has the potential to provide benefits to individuals and reduce the burden of disease and public health expenditure. Similarly, just 10 percent of the articles (three out of 29) expressed concerns about the negative impact that PES may have on the child-parent relationship by causing relational asymmetries between generations and limiting the autonomy of the future child.

CONCLUSION

Our content analysis has shown that the media discourse on PES and the birth of baby Aurea has been highly influenced by expert opinion. In fact, leading experts from bioethics and a range of other academic disciplines contributed 38 percent of the content in the form of blogs, opinion articles, and commentaries, published on prestigious bioethics fora and in the popular press. Furthermore, as our analysis has shown, science reporters have heavily relied on expert opinion in writing stories about the ethical challenges and societal implications of PES. One important finding of our study is the prevalence of negative attitudes towards the technology, as opposed to past media representations of PES, which had been neutral towards the technology.\textsuperscript{26} This change in attitudes is likely caused by the amplified voices of bioethics experts reacting to the first clinical use of the technology, which made hypothetical ethical dilemmas a very real possibility. As far as the thematic focus of media representations is concerned, the birth of the first baby using PES has raised ethical concerns similar to those highlighted in the literature on PES and embryo selection through pre-implantation genetic diagnosis, with the most prominent issue being the absence of robust scientific evidence for the predictive accuracy of PRS modeling and its practical value in IVF settings. Although the critical nature of media discourse can contribute to raising public awareness about the ethical acceptability of the technology, bioethicists should also examine the effect of economic forces and societal pressures to have a perfect child that may be driving prospective parents to seek such unproven genetic interventions. PES is an emerging niche in a large, unregulated market for genetic testing services that has
the potential to shape the future of reproductive medicine, and there is an urgent need for a policy debate on how it can be developed responsibly and ethically.

1 J. Habermas, "The Debate on the Ethical self-Understanding of the Species," The Future of Human Nature (Oxford, UK: Blackwell Publishing, 2003): p. 16-100.

2 Polygenic risk scores (PRS) are used in personalized medicine to predict disease risk in different human populations, not necessarily for risk modelling in embryos. Polygenic embryo screening (PES), on the other hand, involves the clinical use of PRS modelling from genome-wide association studies of adult populations for selecting embryos with the lowest probability of developing certain health conditions in adulthood. It could potentially be used to select embryos with a higher probability for inheritance of certain physical traits or complex characteristics.

3 C. Goldberg, "Picking Embryos With Best Health Odds Sparks New DNA Debate," Bloomberg September 17, 2021.

4 D. Conley, "A new age of genetic screening is coming — and we don’t have any rules for it," The Washington Post June 14, 2021.

5 K. Kamenova, A. Reshef, and T. Caulfield, "Angelina Jolie's faulty gene: newspaper coverage of a celebrity's preventive bilateral mastectomy in Canada, the United States, and the United Kingdom," Genetics in Medicine 16, no. 7 (2014): 522-28.

6 K. Kamenova et al., "Media portrayal of non-invasive prenatal testing: a missing ethical dimension," Journals of Science Communication 15, no. 2 (2016): 1-19.

7 B. Talat, Choosing the "Smartest" Embryo: Embryo Profiling and the Future of Reproductive Technology, (Canadian Institute for Genomics and Society, March 14, 2019), https://www.genomicsandsociety.com/post/choosing-the-smartest-embryo-embryo-profiling-and-the-future-of-reproductive-technology.

8 E. Parens, S. P. Applebaum, and W. Chung, "Embryo editing for higher IQ is a fantasy. Embryo profiling for it is almost here.," Statnews, February 12, 2019.

9 T. Pagnaer et al., "Polygenic risk scoring of human embryos: a qualitative study of media coverage," BMC Medical Ethics 22, no. 1 (2021): 1-8.

10 E. L. de Zeeuw et al., "Polygenic scores associated with educational attainment in adults predict educational achievement and ADHD symptoms in children," American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics 165b, no. 6 (2014): 510-20.

11 A. Okbay et al., "Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses," Nature Genetics 48, no. 6 (2016): 624-33.

12 F. Ray, "Embryo Selection From Polygenic Risk Scores Enters Market as Clinical Value Remains Unproven," (December 22, 2021). https://www.genomeweb.com/sequencing/embryo-selection-polygenic-risk-scores-enters-market-clinical-value-remains-unproven#.YeVWzvhOk2w.

13 J. Savulescu, "The moral case for eugenics?," IAI News, September 28, 2021, https://iai.tv/articles/the-moral-case-for-eugenics-auid-1916.

14 S. Munday and J. Savulescu, "Three models for the regulation of polygenic scores in reproduction," Journal of Medical Ethics 47, no. 12 (2021): 1-9.

15 F. Forzano et al., "The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice," European Journal of Human Genetics (2021).

16 Forzano et al., 1-3; P. Turley et al., "Problems with Using Polygenic Scores to Select Embryos," The New England Journal of Medicine 385, no. 1 (2021): 78-86.

17 N. J. Wald and R. Old, "The illusion of polygenic disease risk prediction," Genetics in Medicine 21, no. 8 (2019): 1705-7.
18 M. J. Sandel, "The case against perfection: what's wrong with designer children, bionic athletes, and genetic engineering," *Atlantic Monthly* 292, no. 3 (2004): 50-4, 56-60, 62.

19 H. Haidar, "Polygenic Risk Scores to Select Embryos: A Need for Societal Debate," *Impact Ethics (blog)*, November 3, 2021, https://impactethics.ca/2021/11/03/polygenic-risk-scores-to-select-embryos-a-need-for-societal-debate/.

20 Pagnaer et al., 1-8.

21 Forzano et al., 1-8.

22 Turley et al., 78-86.

23 P. Ball, "Polygenic screening of embryos is here, but is it ethical?," *The Guardian*, October 17, 2021.

24 W. K. Davis, "A New Kind of Embryo Genetics Screening Makes Big Promises on Little Evidence," *Slate*, July 23, 2021, https://slate.com/technology/2021/07/prs-model-snp-genetic-screening-counseling.html.

25 J. Savulescu, "Procreative beneficence: why we should select the best children," *Bioethics* 15, no. 5-6 (2001): 413-26.

26 Pagnaer et al., 1-8.