Human Gene Therapy

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A need for better understanding is the major determinant for public perceptions of human gene editing.

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ABSTRACT:

BACKGROUND: The CRISPR/Cas system could provide an efficient and reliable means of editing the human genome and has the potential to revolutionise modern medicine; however, rapid developments are raising complex ethical issues. There has been significant scientific debate regarding the acceptability of some applications of CRISPR/Cas, with leaders in the field highlighting the need for the lay public's views to shape expert discussion. As such, we sought to determine the factors that influence public opinion on gene editing.

METHOD: We created a 17-item online survey translated into 11 languages and advertised worldwide. Topic modelling was used to analyse textual responses to determine what factors influenced respondents' opinions towards human somatic or embryonic gene editing, and how this varied between respondents with differing attitudes and demographic backgrounds.

RESULTS: A total of 3,988 free text responses were analysed. Respondents had a mean age of 32 (11-90) and 37% were female. The most prevalent topics cited were '*Future Generations*', '*Research*', '*Human Editing*', '*Children*', and '*Health*'. Respondents who disagreed with gene editing for health-related purposes were more likely to cite the topic '*Better Understanding*' than those who agreed to both somatic and embryonic gene editing. Respondents from 'Western' backgrounds more frequently discussed '*Future Generations*', compared to participants from 'Eastern' countries. Religious respondents did not cite the topic '*Religious Beliefs*' more frequently than non-religious respondents, while Christian respondents were more likely to cite the topic '*Future Generations*'.

CONCLUSIONS: Our results suggest that public resistance to human somatic or embryonic gene editing does not stem from an inherent mistrust of genome modification, but rather a desire for greater understanding. Furthermore, we demonstrate that factors influencing public opinion vary greatly amongst demographic groups. It is crucial that the determinants of public attitudes towards CRISPR/Cas are well understood so that the technology does not suffer the negative public sentiment seen with previous genetic biotechnologies.

KEYWORDS

CRISPR/Cas, Public Perception, Text Mining, Gene Editing, Global Survey,

DECLARATIONS

Ethics approval and consent to participate

Ethics approval for this research was obtained from the Monash University Human Research Ethics Committee (MUHREC - CF15/1606).

Consent to publish

Not applicable

Availability of data and materials

Data and scripts are available on request.

Competing interests

No Authors have any conflicts of interest related to this work.

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Authors' Contributions

Conceptualization, T.M., E.F., G.R., C.M., and A.W.H.; Methodology, T.M., L.F., L.S., H.H.L, and A.W.H.; Software, G.E.C.G. and D.M.B., T.B.; Formal Analysis, P.G.S., D.M.B., T.B. and A.W.H.; Resources, C.C., H.H.L. and A.P.; Writing – Original Draft, T.M, and D.M.B.; Writing – Review & Editing, L.F., E.F., G.R., C.M., L.S., C.C., H.H.L., T.B., A.P., and A.W.H.; Visualization, D.M.B. and T.B. Supervision, A.P. and A.W.H.; Funding Acquisition, C.C., A.P., T.B. and A.W.H.

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MAIN TEXT:

BACKGROUND:

The adaptation of the Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) and CRISPR-associated protein (Cas) system has potential to be the first accurate and easily accessible means of editing the human genome. Whilst ongoing breakthroughs appear set to provide cures to previously untreatable genetic conditions,[1–3] there are concerns whether all such applications are ethically permissible [4,5]. Embryonic gene editing could be used to alter non-health-related traits such as physical appearance or intelligence, and embryonic editing would affect the human germline, causing heritable genome modifications. The controversy surrounding accurate embryonic gene editing has caused significant debate amongst scientists and the wider public. Despite this, a global consensus has not been reached on the acceptability of some applications. Whilst expert opinion varies, it is well established that there must be broad moral consensus on the issue and scientific discourse must consider the views of the public [6–8].

Given the paucity of research exploring public attitudes towards CRISPR/Cas technology, we conducted an online survey of 12,562 participants from 185 countries exploring public attitudes towards human gene editing [9]. This work highlighted firm support for gene editing for health-related purposes in somatic and embryonic cells, with decreased support for its use for eugenic manipulation. Critically, as part of this survey, respondents were asked to share the reasons for their opinions and what factors influenced this. Using this textual data, we aimed to determine what factors influence respondents' attitudes towards human gene editing.

METHODS:

Questionnaire Development and Administration:

To gauge public opinion, we developed a 17-item online questionnaire (Sup Table 1) [9]. The first section of the questionnaire recorded de-identified demographic details such as gender, religion, ethnicity, country of residence, education, financial status and whether participants were personally affected by genetic disease. Financial status was generally

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defined by a self-reported financial standing of being below, average or above-average wealth. The second section asked participants their opinions on the application of gene editing including its use in somatic cells and embryos for life threatening and debilitating diseases. Participants were also asked their attitudes towards embryonic editing for non-health-related purposes such as to alter physical appearance, intelligence or sporting ability. This section employed a five-point Likert scale from "strongly agree" to "strongly disagree"; with an additional option of 'I don't know'. These questions were accompanied with an explanatory paragraph defining key terms such as 'life threatening', 'debilitating' and 'embryo', and outlined the heritable nature of embryonic gene editing. Finally, one free-text open-ended question was used to assess the determinants of participants' attitudes: "*We are also interested in understanding the reasons for your answers. Please describe the factors that have influenced your response or attitude towards human gene engineering.*"

The questionnaire was refined using a thinking-aloud cognitive phase testing – a tool where people are asked to take the questionnaire and then interviewed to check their understanding of each question and to ensure multiple participants interpret the questions in the same way [10]. This testing was undertaken in ten English speaking people. Changes were made iteratively to two of the application questions and the explanatory paragraph, with no changes deemed necessary to the final open-ended question. The final English questionnaire was then translated into Arabic, Chinese, French, German, Hindi, Japanese, Portuguese, Russian, Spanish and Turkish. To ensure consistency across the questionnaires, a separate translator then back translated each language with changes made as appropriate. The questionnaires were then formatted and placed onto an online platform and completed by a third translator prior to dissemination.

The questionnaire was launched online in June 2015. At this time, we began advertising on social media through Facebook, Twitter and Google. A separate questionnaire was formatted for WeChat, which is one of the commonly used social media applications in China, to enable dissemination in China, where Twitter, Facebook and Google promotions are restricted.

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Data Preparation and Text Cleaning:

Survey responses were collated before being translated back into English. Data preparation and analyses were performed in the R statistical environment (version 3.1.2) and Python (version 3.4.3). All data and scripts are available at https://github.com/hewittlab/Gene_Edit_Survey.

We used descriptive statistics to summarize demographic features of respondents. Given the likelihood of spurious responses, participants with extremes in reported age, below 10 and above 90 years, were dropped (n=141). For dependent variables, we collapsed the Likert scale to a three-point scale ('disagree', 'neutral', 'agree') initially merging the 'neutral' and 'I don't know' response categories. For each participant in the survey, where possible, we retrieved geolocation data. IP addresses were queried using a function in R to return location data (country, region/state, longitude and latitude, etc.) from freegeoip.net, a freely available HTTP application-programming interface. Geolocate data were not available for 1,362 participants. Duplicate IP addresses were reviewed and there were a total of 10,564 unique sites.

To allow meaningful textual analysis on the free text responses, the responses were initially cleaned before processing. As the free text data was UTF-8 encoded and entered in multiple languages, we translated the non-English responses into English with the use of Google Translate [11,12]. After translation, we removed "Internet Slang", such as "lol" (Laugh out loud) and "idk" (I don't know), and substituted in their full equivalent. We also performed automated spelling correction on the now translated and slang-free text. The spelling correction algorithm (norvig.com/spell-correct.html) used a corpus of 1300 English books downloaded from the Gutenberg Project (gutenberg.org) along with the UNIX words file.

Data Analyses:

Topic modelling is a soft clustering method based on the identification of latent topics (in the form of multinomial distributions over words) based on document-level co-occurrence. Of the 12,562 survey respondents, 3,935 provided textual response to the final open-ended question and were used as the basis for topic modelling, taking a single response as

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a "document". Topic modelling was performed using the Mallet [13] implementation of latent Dirichlet allocation, with models trained for user-defined number of topics T = (15, 20, 25, 30, 40, 50). Optimisation was performed using an average normalised pointwise mutual information objective function [14] and yielded 25 as the optimal assignment of T. The resultant 25 topics were further pruned to 16 by applying two criteria: (1) topics that were allocated to small numbers of documents were removed (based on a topic prior of < 0.1); and (2) topics with low model precision were removed, based on the automatic injection and subsequent detection of 'intruder words', as described by Lau et al. [14]. The final list of 16 topics and their constituent words are provided in Table 1. We then determined the topic proportions for different partitions of the data, based on demographic variables and yes-no responses to particular questions. Statistical significance for differences in topic proportions over particular sub-populations (of x individuals) was determined by generating a null distribution (no enrichment) of composition scores for 1,000,000 sub-populations of x individuals sampled with replacement from the full set of respondents. A non-parametric p-value was calculated from this distribution using an empirical cumulative distribution function approximation with a default pseudocount of 1 [15].

RESULTS:

Following curation of nonsensical answers, a total of 3,935 free text responses were analysed from 185 countries. The mean age of these respondents was 32 years (11-90) and 1,464 (37.2%) were female. 1,794 (45.6%) reported a religious affiliation, 921 (23.4%) had worked in healthcare and 1,790 (45.5%) had received a tertiary education. Only 476 (12.1%) had not heard of gene editing prior to the survey, whilst 1,291 (32.8%) had significant prior knowledge. The breakdown of responses to each question relating to the application of somatic or embryonic gene editing is provided in Fig. 1.

The most prevalent topics found on text analysis included '*Future Generations*', '*Research*', '*Human Editing*', '*Children*', and '*Health*' (Fig. 2, Tab 1). Respondents who were against gene editing for health-related purposes in somatic cells, showed a higher use of the words associated with '*Better Understanding*' than people who agreed to gene editing for

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this purpose (P<0.001). By comparison, participants who disagreed with gene editing for health-related purposes did not refer to topics such as '*Religious Beliefs'* and '*Natural Selection'* more frequently. For questions related to embryonic gene editing, '*Better Understanding'* was again over-represented (P<0.001), rather than topics like '*Future Generations'* or '*Children*'. In contrast, for genetic editing of non-health-related traits, respondents who agreed were less likely to discuss '*Future Generations'* and more likely to cite the topic '*Children'* in their responses compared to those who disagreed (P<0.001).

Respondents from different demographic backgrounds were more likely to discuss certain topics in their responses. People from 'Western' countries, such as the United Kingdom (UK) and Australia, more frequently discussed '*Future Generations'*, while this was less frequently cited amongst respondents from 'Eastern' countries such as Japan and China (P<0.001, Sup Fig. 1). French respondents most commonly discussed the topic '*Children*' and were less likely to comment on '*Future Generations*' (P<0.001*).* Chinese respondents more frequently discussed the topic '*Better Understanding*' (Sup Fig. 1) and respondents from both China and Japan were less likely to raise the topic '*Future Generations'* (P<0.001*)* compared to those from other countries. Respondents from the UK and South Africa were less likely to discuss the topics *'Research'* and *'Children'.* These changes in topic prevalence between countries were reflected in analysis by self-reported ethnicity. Respondents who identified as European Caucasians were more likely to discuss '*Future Generations'*, while respondents who identified as North and South East Asian were less likely to discuss this topic (P<0.001). Conversely, *'Research'* was under-represented amongst European Caucasians and over-represented amongst South East Asian respondents (P<0.001).

Christian respondents were more likely to discuss '*Future Generations'* while respondents of the Islamic faith were more likely to discuss '*Research*' (P<0.001, Sup Fig. 2). Respondents with no self-reported religious affiliation were less likely to discuss the topic '*Research*' (P<0.001). The topic '*Religious Beliefs'* was equally mentioned amongst religious and nonreligious respondents. Participants who had substantial prior knowledge of gene editing were less likely to discuss '*Future Generations'* in their responses and more likely to

discuss the topic of '*Children*' (P<0.001, Sup Fig. 3). Gender and economic background had no significant impact on the determinants of respondents' opinions towards gene editing.

DISCUSSION:

Our previously published findings indicate that whilst there is firm agreement with the use of human gene editing for health-related purposes, at approximately 60%, this support is far from universal [9]. Importantly, topic modelling highlights the over-representation of the topic '*Better Understanding'* amongst respondents who disagreed with health-related applications, suggesting that propensity to disagree may arise from a desire for better understanding of the technological features and potential risks, rather than a resistance to the concept of gene modification in itself. Although, there is little empirical evidence supporting the deficit-model approach to public engagement [16], the experimental nature, imminent clinical translation and complex ethical issues associated with genome modifications may mean that public education is of great significance in this area. Leading researchers have raised the need for early and thorough public engagement [6,17], and our findings further emphasise the importance of this.

Despite strong opposition from the scientific community towards embryonic gene editing [4,6,17,18], our findings demonstrate similar levels of agreement for both embryonic and somatic cell editing amongst our respondents [9]. Interestingly, for respondents with contrasting opinions regarding embryonic gene editing for health-related purposes, the topic of '*Future Generations'* and '*Children*' were mentioned with similar frequency. However, participants who disagreed with embryonic editing for non-health-related purposes were more likely to discuss '*Future Generations*'. Respondents who agreed with embryonic gene editing for non-health-related purposes were more likely to discuss '*Children*', and less likely to cite '*Future Generations',* perhaps indicating that these participants are considering only the immediate benefits to individual families and children, rather than the potentially negative impact that widespread human enhancement could have on future humanity. In support of this, a recent study by Hendriks and colleagues found that the immediate benefits to individuals and their children's quality of life was the number one reason respondents were in favour of

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genome modification, whilst those opposed were concerned about the negative long-term consequences for society as a whole [19].

Religious affiliation was associated with an increased resistance towards all applications of gene editing, particularly amongst Christian respondents [9]. This is consistent with previous research highlighting markedly lower support for genome editing amongst religious individuals [20]. Interestingly, these respondents were no more likely to discuss the topic of '*Religious Beliefs'* in their free-text responses compared to non-religious respondents (Sup Fig. 2). Instead, Muslim respondents were more likely to discuss the topic '*Research*', whilst Christians more frequently discussed '*Future Generations'*. This perhaps indicates that the resistance Christian respondents have shown towards all applications of gene editing is not a product of the concept of genome modification contradicting Christian doctrine, but instead a result of values arising from living in a Christian environment, which culturally places special emphasis on embryos and other body parts [21]. More focused research will be required to gain deeper understanding of the beliefs and other influencing factors behind this.

Text analysis found the topic '*Research*' over-represented in respondents who reported that they were of Asian ethnicity, and the topic of '*Better Understanding'* over-represented amongst respondents from China. In contrast, respondents from Australia and the UK were more likely to discuss '*Future Generations*'. This may indicate a differing in priorities across countries when assessing the acceptability of new biotechnologies. It appears that the opinions of respondents from 'Western' countries are shaped by the impact of embryonic gene editing on future generations, while generally, 'Eastern' respondents were more greatly influenced by the progress of research and ensuring technical proficiency.

Topic modelling provides a valuable means of interpreting high volume textual data to derive associations and meaning. Of course, the demographic classifications we have used represent highly heterogeneous groups, with a variety of motivations and influencing factors that cannot be captured with one opened ended question. As such, our results represent general trends across broad demographics, and further in-depth investigation, with focus groups and in-depth interviews, will be required to better understand the

attitudes of each demographic group. Furthermore, despite the large-scale collection enabled by online surveys, this collection method also has obvious limitations and recruitment biases, such as a lack of exposure to people not on social-media [22], and in our study, a gender bias favouring male respondents.

CONCLUSION

With the rapid progress of CRISPR/Cas, clinical translation appears imminent. As such, it is imperative that the scientific community endeavour to understand public attitudes towards genome engineering to avoid research being impeded by ethical controversy. Importantly, our findings show that respondents who disagreed with health-related somatic or embryonic gene editing did so because of a desire for greater understanding, rather than a personal sensitivity towards the technological features. Furthermore, we found that the factors influencing opinions varied considerably across different regions and cultural backgrounds. These global trends highlight the need for further in-depth analysis of specific socio-economic groups. Understanding the influencing factors on public opinion towards gene editing is vital in guiding political policy and planning effective public education. Further research in this area will ensure that CRISPR/Cas does not suffer the same varied sentiment suffered by other genetic biotechnologies.

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LIST OF ABBREVIATIONS

CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
Cas	CRISPR Associated Protein
UK	United Kingdom

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TABLE 1

List of topics derived from the topic model and their constituent words

Topic	Word Groupings
Future generations	**future generations generation diseases cells healthy present hope passed passing stage avoid effect family growth testing diabetes members embryonic congenital**
Research	**research science knowledge genetics lot medical scientific field progress personal subject interested work important medicine ethics biology information experience study**
Human editing	**gene editing human genes genome dna consequences lead therapy allowed risk topic specific feel slope slippery cancer highly theory type**
Children	**child children embryos person embryo born parents choice healthy feel make choose sick people happy live birth consent decision condition**
Health	**technology health benefit issues society mankind potential science problem advances benefits safe social humanity ethical conditions issue huge care risk**
Good/bad	**good thing things bad feel idea create great make dangerous wrong possibility personally extent works based kind scientists pretty evil**

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Curing disease	**disease people don't diseases cure agree prevent debilitating alter humans disagree gene wrong altering strongly genetically reason means person individual**
Life	**people live lives family love die normal inherited conditions hand years disabled opinion longer heart friends full job son died**
Physical/mental traits	**physical purposes society mental question cosmetic provided control worth intellectual image methods called survey breakthrough correct profit controlled political ideals**
Changing genes	**genes change time changing genetics changed hereditary offspring appearance peoples mind affect healthier left great learn knowledge edit body features**
Quality of life	**life quality improve suffering threatening save characteristics lives reasons health physical cosmetic pain agree ability debilitating reduce important altering changing**
Better understanding	**understand feel humans understanding benefits concerns risks fully history cons outweigh complex worth blood pros dangerous improvement generally power logical**
Genetic engineering	**genetic engineering disease diseases gene modification treatment change problems medical support reason result babies order eliminate designer future treat diversity**
Natural selection	**nature natural selection evolution human environment traits respect survival species variety evolutionary mess medicine interfere manipulating laws adapt interfering defects**

GM food	**food genetically modified foods crops eat plants modifying natural amos engineered plant animals grow qualities produce feed products countries opposed**
Religious beliefs	**religious population beliefs view moral views back catholic point due increasingly faith responses science speak vast follow reached professional event**

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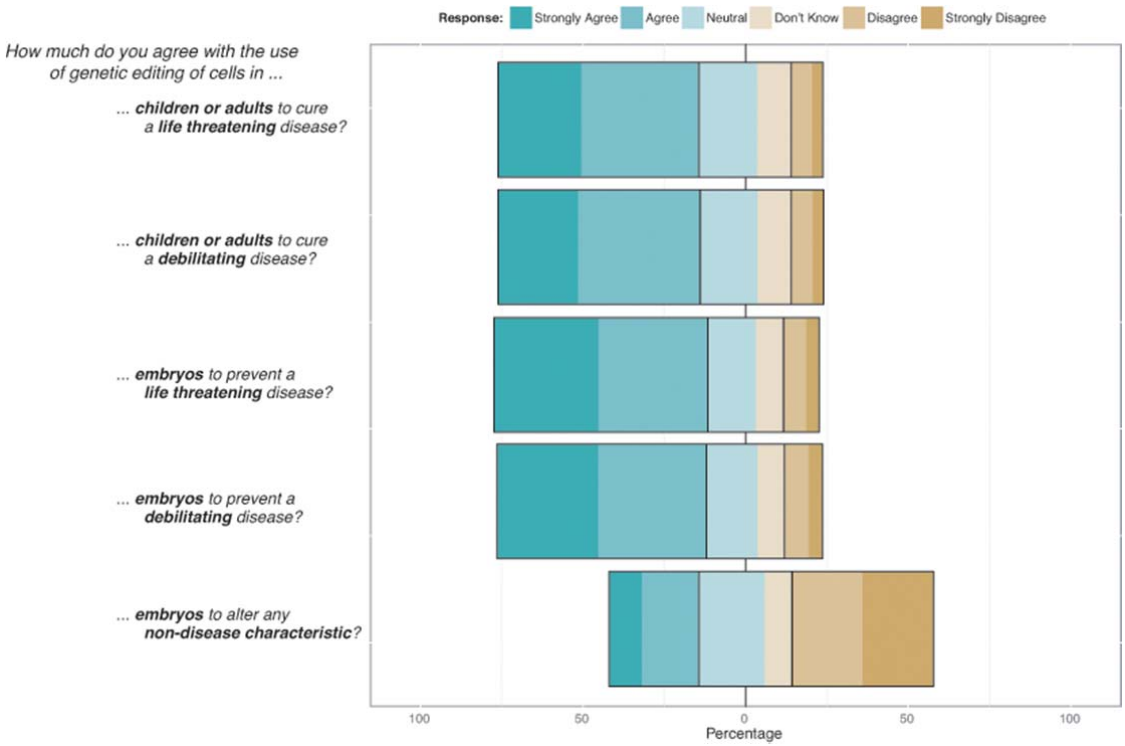

FIGURE 1

Proportion of responses to questions relating to the application of human gene editing. Questions are displayed in the order presented to participants as outlined in Supplementary Table 1, and responses were divided across a five-point Likert scale. "Strongly Agree" and "Agree" as well as "Strongly Disagree" and "Disagree" were collapsed for analysis. "Neutral" and "I Don't Know" responses have been merged.

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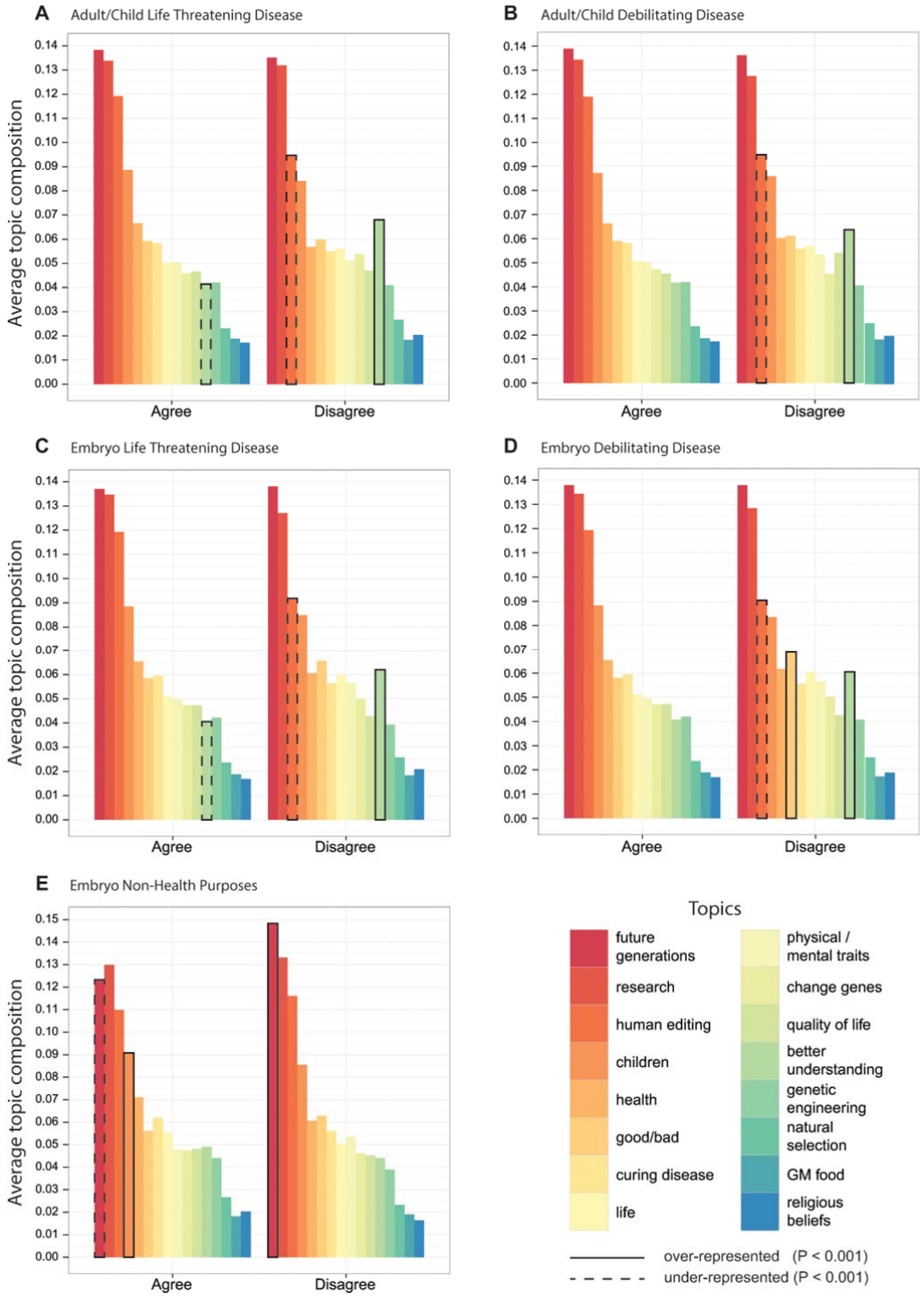

FIGURE 2

Breakdown of topic models for the free-text responses. People were asked to outline the reasons for their opinions on applications of gene editing. Each topic comprises of a list of

co-occurring words as defined in Table 1, and topic composition is compared between respondents who agreed with each question and those who disagreed. Use of gene editing (**A**) to cure life threatening diseases in adults and children; (**B**) to cure debilitating diseases in adults and children; (**C**) to prevent life threatening diseases in embryos; (**D**) to prevent debilitating diseases in embryos; (**E**) to alter non-health-related traits. A non-parametric p-value was calculated using an empirical cumulative distribution function approximation.

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SUPPLEMENTARY TABLE 1:

Survey items used in the English online questionnaire.

1	What is your sex?
2	What year were you born in?
3	What country do you live in
4	What is your ethnic background / origin?
5	Do you have a religious affiliation?
5.1*	What is your religious affiliation?
6	What is your highest level of education?
7	Have you ever worked in a health or medical related field?
7.1*	What have you worked as?
8	Have you ever heard of human genetic engineering or gene editing?
9	How would you describe your financial situation?
10	Do you or anyone in your family have an inherited or genetic condition?
10.1*	Who is affected?
10.2*	What is the disease?

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11	How much do you agree with the use of genetic editing of cells in **children or adults** to cure a **life threatening disease**? This means the disease could still be passed on to their children.
12	How much do you agree with the use of genetic editing of cells in **children or adults** to cure a **debilitating disease**? This means the disease could still be passed on to their children.
13	How much do you agree with the use of genetic editing of cells in **embryos** to prevent a **life threatening disease**? This means that all future generations would not have the disease.
14	How much do you agree with the use of genetic editing of cells in **embryos** to prevent a **debilitating disease**? This means that all future generations would not have the disease.
15	How much do you agree with the use of genetic editing of cells in **embryos** to alter any **non-disease characteristic** - such as memory, eye colour or height? This would mean that all subsequent generations would have the same genetic characteristics.
15.1*	If you could safely genetically edit your embryo would you use this technology to determine **physical appearance** (eye colour; hair colour; skin colour)?
15.2*	If you could safely genetically edit your embryo would you use this technology to determine **intelligence**?
15.3*	If you could safely genetically edit your embryo would you use this technology to determine **strength or sporting ability**?
15.4*	What other non-health related traits would you edit?

16	How much do you agree with the use of **genetically modified food**?
17	We are also interested in understanding the reasons for your answers. Please describe the factors that have **influenced your response** or attitude towards human gene engineering.

* Question only appeared to some respondents depending on their answer to the previous question

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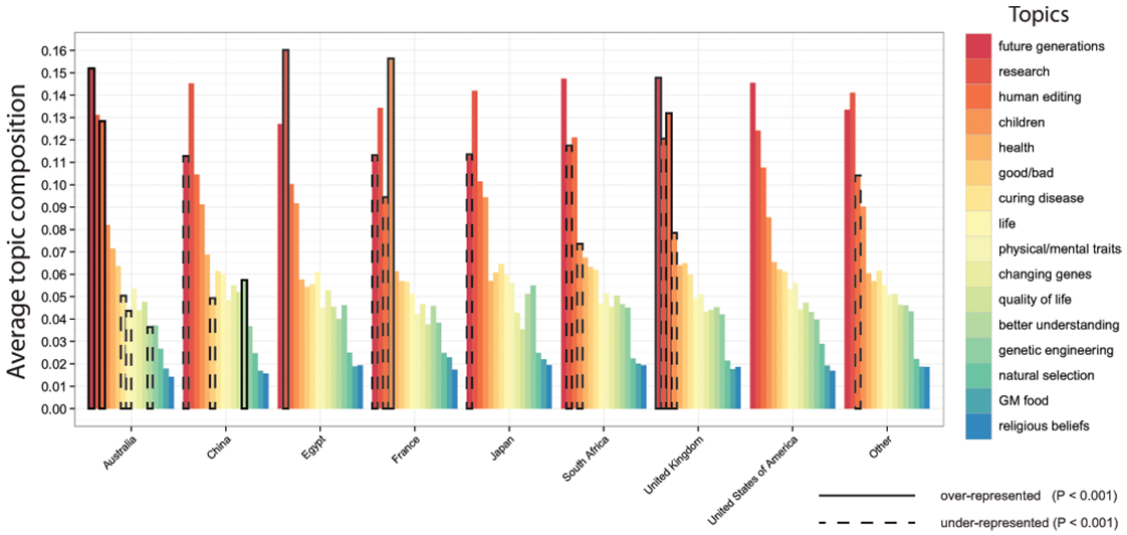

SUPPLEMENTAL FIGURE 1

Breakdown of topic models for the free-text responses separated by country. People were asked to outline the reasons for their opinions on applications of gene editing. Each topic comprises of a list of co-occurring words as defined in Table 1, and topic composition is compared between respondents from different countries.

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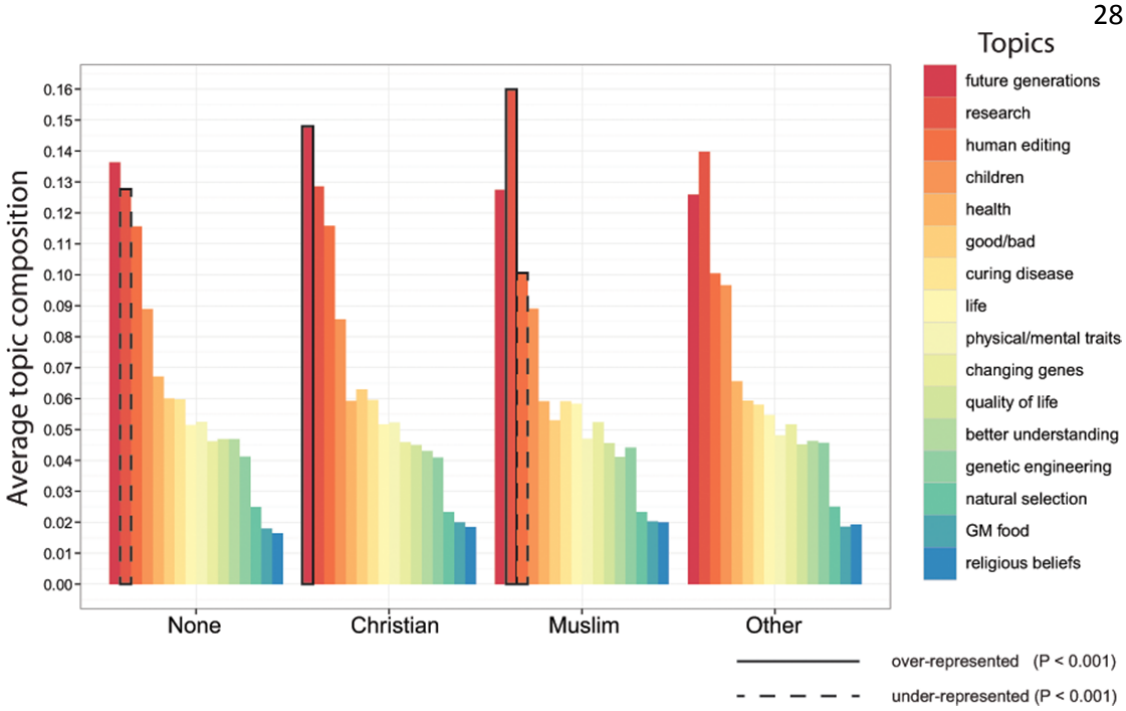

SUPPLEMENTAL FIGURE 2

Breakdown of topic models for the free-text responses separated by religion. People were asked to outline the reasons for their opinions on applications of gene editing. Each topic comprises of a list of co-occurring words as defined in Table 1, and topic composition is compared between respondents from different self-reported religions.

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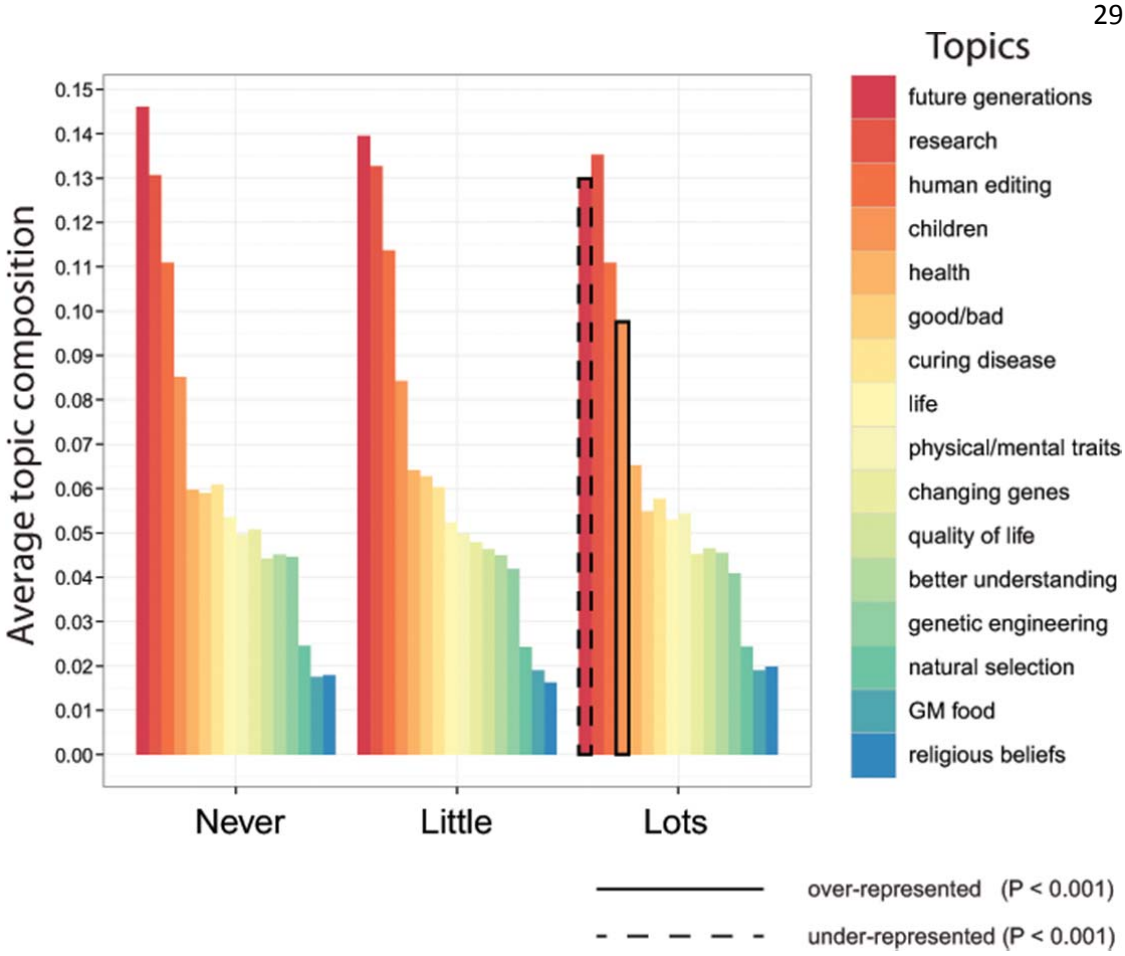

SUPPLEMENTAL FIGURE 3

Breakdown of topic models for the free-text responses separated by the amount people had previously heard about human genetic engineering or gene editing. People were asked to outline the reasons for their opinions on applications of gene editing. Each topic comprises of a list of co-occurring words as defined in Table 1, and topic composition is compared between respondents who had previously never heard about human gene editing, or had heard about it a “little” or “lots”.