Human Gene Therapy

DOI: 10.1089/hum.2020.136

Title: Gene editing for treatment and prevention of human diseases: a global survey of gene editing-related researchers

Short title: Gene editing for treat and prevent diseases

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Abstract

In the next decades, gene editing technologies are expected to be used in the treatment and prevention of human diseases. Yet, the future uses of gene editing in medicine are still unknown, including its applicability and effectiveness to the treatment and prevention of infectious diseases, cancer, monogenic, and polygenic hereditary diseases. This study aims to address this gap by analyzing the views of over one thousand gene editing-related researchers from all over the world. Some of our survey results show that, in the next ten years, DNA double-strand breaks are expected to be the main method for gene editing and CRISPR-Cas Systems to be the mainstream programmable nuclease. In the same period, gene editing is expected to have more applicability and effectiveness to treat and prevent infectious diseases and cancer. Off targeting mutations, reaching therapeutic levels of editing efficiency, difficulties in targeting specific tissues in vivo, regulatory, and ethical challenges are among the most relevant factors that might hamper the use of gene editing in humans. In conclusion, our results suggest that gene editing might become a reality to the treatment and prevention of a variety of human diseases in the coming ten years. If the future confirms these researchers' expectations, gene editing could change the way medicine, health systems, and public health deal with the treatment and prevention of human diseases.

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Introduction

Gene editing technologies are considered a major evolution in the field of genetic engineering. Its development has made possible the realization of new forms of genetic alterations - such as addition, correction, substitution, and ablation - that permanently alter the DNA sequence to insert desired mutations [1–3]. With its continuous development, gene editing technologies have proven promising for a wide range of activities, such as medicine, agriculture, and food production [4,5]. The emergence of gene editing has become possible with the development of programmable nucleases, which are customized proteins capable of acting on very specific parts of DNA with great precision [2].

The first programmable nuclease used for editing human cells was Meganuclease, first used in 1994. Since then other programmable nucleases have been used for this purpose. Zinc Finger Nucleases (ZFN) was first used in 2003 and Transcription Activator-Like Effector Nuclease (TALEN) in 2011. More recently, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology was used for the first time in 2013. Today, CRISPR is often regarded as the most promising programmable nuclease for human cell edition [3,6] and thus for the treatment of diseases [7]. By presenting characteristics such as low production cost, ease of handling, and high specificity in gene editing, CRISPR has become the most popular programmable nuclease among geneticists around the world [4].

In the future, it is hoped that gene editing technologies can be applied to a wide variety of diseases - such as cancer, infectious viral, cardiovascular, hematological, immunological, muscular dystrophy, respiratory [7] –, giving rise to expectations that they may trigger a new era in the treatment and prevention of human diseases [6]. However, the use of gene editing for such purposes still depends on overcoming several scientific and technological challenges. Among the most important challenges are (i) achieving therapeutic levels [1,8]; (ii) reduction of off-targeting mutations [1,3,8–11]; (iii) patient's immune system responses to repeated treatments [1,6,8,9,12,13]; (iv) and difficulties in reaching specific tissues in vivo [1,8,9].

One can, therefore, consider that the future of gene editing for the treatment and prevention of human diseases is still quite uncertain. Few studies have sought to anticipate future possibilities related to the use of gene editing technologies for the treatment and prevention of human diseases [14–17], and none explored the different possibilities of application of the various programmable nucleases (Meganuclease, ZFN, TALEN, LEAPER,

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and CRISPR) for treatment and prevention of various types of human diseases (cancer, infectious diseases, and hereditary monogenic and polygenic diseases). Our study addresses this gap by assessing the views of gene editing-related researchers from all over the world, who took part in a web-based survey. They are authors of recent scientific publications related to gene editing, indexed in the Web of Science Core Collection (WoS). By identifying the expectations of over one thousand gene editing researchers from around the world, our study offers a more comprehensive view of the future of gene editing for the treatment and prevention of human diseases.

Materials and Methods

A systematic literature review was performed from scientific publications related to gene editing, indexed in WoS. The publications were identified using the following search strategy:

TI=("genes edit*" or "genes engineer*" or "genes therap*" or "genes treatment*" or "genes enhanc*" or "genes repair*" or "genes replacement*" or "genes Intervention*" or "genes insertion*" or "gene edit*" or "gene engineer*" or "gene therap*" or "gene treatment*" or "gene enhanc*" or "gene repair*" or "gene replacement*" or "gene Intervention*" or "gene insertion*" or "genom* edit*" or "genom* engineer*" or "genom* therap*" or "genom* treatment*" or "genom* enhanc*" or "genom* repair*" or "genom* replacement*" or "genom* Intervention*" or "genom* insertion*" or "genetic* edit*" or "genetic* engineer*" or "genetic* therap*" or "genetic* treatment*" or "genetic* enhanc*" or "genetic* repair*" or "genetic* replacement*" or "genetic* Intervention*" or "genetic* insertion*" or "deoxyribonucleic acid edit*" or "deoxyribonucleic acid engineer*" or "deoxyribonucleic acid therap*" or "deoxyribonucleic acid treatment*" or "deoxyribonucleic acid enhanc*" or "deoxyribonucleic acid repair*" or "deoxyribonucleic acid replacement*" or "deoxyribonucleic acid Intervention*" or "deoxyribonucleic acid insertion*" or "dna* edit*" or "dna* engineer*" or "dna* therap*" or "dna* treatment*" or "dna* enhanc*" or "dna* repair*" or "dna* replacement*" or "dna* Intervention*" or "dna* insertion*") AND TS=((therap* or treat* or prevent*) NEAR/1 diseas*)
AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Review) INDEXES=SCI-EXPANDED TIMESPAN=2014-2019

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To include recent research results, we set the query to retrieve only articles or review articles published between 2014 and September 2019. Only publications written in English were considered so the authors could be able to perform the literature review –98% of all gene editing-related publications were written in English. Natural science publications are best suited for this type of study, where the aim is to foresee future uses of a given technology [18–20]. To prioritize these publications, we included only the Science Citation Index Expanded (SCI-Expanded) – 99% of all gene editing-related publications were indexed in the SCI-Expanded. The search strategy covered two parts. The first one contains descriptors related to gene, engineering, treatment, and therapy, identified in the Medical Subject Headings (MeSH), U.S. National Library of Medicine (https://www.ncbi.nlm.nih.gov/mesh). Six gene terms (genes, genom*, genetic*, deoxyribonucleic acid, dna*) and nine engineering, treatment, and therapy terms (edit*, engineer*, therap*, treatment* enhanc*, repair*, replacement*, intervention*, insertion*) were selected. Combined, they resulted in 54 distinct expressions. The second part has descriptors related to therapy, treatment, and prevention near the term disease(s) - for example, "prevention of diseases". In WoS advanced search mode, these two parts were combined to identify publications that (1) contained at least one of the 54 expressions in their titles (TI) and (2), at the same time (AND), one or more terms related to therapy, treatment and prevention near (NEAR/1) to the term disease(s), occurring in the title, abstract or keywords of the articles (TS).

Performed in September 2019, the search returned 219 articles or review articles. We made a pre-selection of these publications by reading their Abstracts. We looked for publications referring to gene editing for the treatment and prevention of human diseases. The 79 pre-selected publications were then imported to the software Citavi 6.3 for full-text reading and reference management. The final list of 39 publications was selected based on relevance to the literature review and development of the questionnaire [1,3,4,6,7,9–15,21–47].

The respondents of this survey are authors of recent scientific publications related to gene editing indexed in WoS. They were identified using the following query:

TS=("genes edit*" or "genes engineer*" or "genes therap*" or "genes treatment*" or "genes enhanc*" or "genes repair*" or "genes replacement*" or "genes Intervention*" or "genes insertion*" or "gene edit*" or "gene engineer*" or "gene therap*" or "gene

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treatment*" or "gene enhanc*" or "gene repair*" or "gene replacement*" or "gene Intervention*" or "gene insertion*" or "genom* edit*" or "genom* engineer*" or "genom* therap*" or "genom* treatment*" or "genom* enhanc*" or "genom* repair*" or "genom* replacement*" or "genom* Intervention*" or "genom* insertion*" or "genetic* edit*" or "genetic* engineer*" or "genetic* therap*" or "genetic* treatment*" or "genetic* enhanc*" or "genetic* repair*" or "genetic* replacement*" or "genetic* Intervention*" or "genetic* insertion*" or "deoxyribonucleic acid edit*" or "deoxyribonucleic acid engineer*" or "deoxyribonucleic acid therap*" or "deoxyribonucleic acid treatment*" or "deoxyribonucleic acid enhanc*" or "deoxyribonucleic acid repair*" or "deoxyribonucleic acid replacement*" or "deoxyribonucleic acid Intervention*" or "deoxyribonucleic acid insertion*" or "dna* edit*" or "dna* engineer*" or "dna* therap*" or "dna* treatment*" or "dna* enhanc*" or "dna* repair*" or "dna* replacement*" or "dna* Intervention*" or "dna* insertion*")

AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-SSH, ESCI Timespan=2014-2019

This is a more comprehensive version of the first search strategy. We used the 54 gene editing-related expressions, all document types, and all citation indexes. Performed in November 2019, the search returned 55,617 records of publications. The complete metadata of all publications was downloaded in txt format and imported into the text and data mining software VantagePoint 11.0, where we created a CSV file containing authors' information (name, email, and publication title). Then, using an in-house Python program, we: (i) pre-processed the publication data; (ii) linked the emails to their owners' names - 38,658 (79.8%) of total 48,439 unique emails were linked; (iii) created CSV files to be uploaded in SurveyMonkey; (iv) and programmed a calendar of invitation and reminder emails to be used in the pilot phase and formal study. After uploading, the number of linked emails was reduced to 36,279 and the number of unlinked emails to 9,271 due to bounced emails and opted-out contacts.

The systematic literature review allowed the identification of three thematic areas on the future of gene editing, which gave rise to the questions of the survey's questionnaire: (i) gene editing technological standards, (ii) technology challenges, and (iii) treatment and prevention of diseases (infectious diseases, cancer, monogenic and polygenic hereditary

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diseases). Auxiliary knowledge level questions on gene editing and its application in the treatment and prevention of diseases were used in the questionnaire. Respondents without knowledge of the subject were disqualified from the survey and did not answer the remaining questions. We opted to not include demographic questions in the survey because respondents' characteristics such as, e.g., age, gender, ethnicity, employment, location, are not expected to influence the results [18–20]. To avoid respondents' fatigue, skipped questions, survey dropout, we set the questionnaire to be answered within 2 to 3 minutes.

Before the formal study, the questionnaire was validated in a pilot study. As known, the customization of invitation emails positively influences the response rates of web-based surveys [48]. Thus, in order not to jeopardize the response rate of the formal study, only the owners of unlinked emails were invited to participate in the pilot phase. All 9,271 researchers with unlinked emails were invited. The pilot study obtained a response rate of 1.48%. The 138 researchers who took part in this phase did not recommend any changes in the questionnaire, so it was not modified for the formal study. Even so, we opted to not include this data in the study's results.

The pilot and the formal study were conducted in December 2019 via SurveyMonkey (surveymonkey.com/). The questionnaire was available for completion for eight consecutive days after the email invitation was sent. During this period, up to three reminder emails were sent to non-responders. Both the questionnaire and the invitation and reminder emails informed the researchers about the survey (including organization conducting the study and its purpose, data collection, and treatment, confidentiality, and privacy, informed consent). Before answering the questionnaire, they were informed that the survey was for research purposes only, personal or sensitive data would not be collected, responses would not be identified, informed consent would be given by answering the questionnaire. Thus, all respondents that participated in this study gave us informed consent to use the data collected. Considering voluntary participation, anonymized responses, and absence of sensitive or personal questions, no examination by an ethics committee was needed.

Figure **1** summarizes the methods.

Figure 1 – Methods

The data collected was exported in Excel format to be analyzed in R using the packages DescTools (cran.r-project.org/web/packages/DescTools/index.html), psych (https://cran.r-project.org/web/packages/psych/index.html), and corrplot statistics (https://cran.r-project.org/web/packages/corrplot/). The confidence intervals of the response estimates were built using simultaneous confidence intervals for multi-nominal distributions [49]. These confidence intervals were used to assess the existence of statistical differences between the two groups of respondents: some knowledge and good knowledge. We also conducted a series of statistical analyses on the relationship between questions using two types of correlation metrics: Cramer's V and Kendall tau. The former was used to measure associations between categorical nominal variables [50], and the latter to measure associations between categorical ordinal variables [51,52]. The confidence intervals of the response estimates and the correlations metrics are available as Supplementary Material. To simplify the description of the results, segmentation by knowledge level will not be presented graphically. When there is a statistical difference between the two groups of respondents, the difference will be highlighted in the description of the results.

We mapped the publications of all qualified respondents and built a two-mode network of authors' keywords and Research Areas (a subject classification scheme used in WoS) to provide a proxy of their research characteristics. The publications were mapped using the VantagePoint 11.0, where we cleaned and standardized the list of authors' keywords, and built the co-occurrence matrices of authors' keywords and Research Areas. These matrices were then imported into the software Gephi 0.9.2, where we built the two-mode network. The network's layout was given by the algorithm Force Atlas 2, and the nodes' sizes reflect their weighted degree (sum of connected nodes weighted by co-occurrence among the nodes). We used eigenvector centrality (EG) to analyze the nodes' centrality in the network. Additionally, using the respondents' email internet protocols, we identified their countries and built a world map depicting the global distribution of respondents. The world map was built using the software Tableau 2019.3.

Limitations of the study

The query applied in the WoS was comprehensive enough to not exclude a priori the target researchers of this study. The target researchers are those with knowledge on gene

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editing and applications of gene editing to the treatment and prevention of diseases. Unfortunately, the respondents' level of knowledge can only be known a posteriori, in the questionnaire, when they answer the auxiliary questions of knowledge level. Thus, on the one hand, by using a comprehensive strategy we reduce the risk of not inviting target researchers – which would probably have occurred if we had used a narrow search strategy (with just a few terms related to gene editing). On the other hand, by potentially including non-target researchers, the survey population is "artificially" enlarged, and this may negatively affect the survey response rate. In part, this is because it is expected that the invitation to participate in the study will primarily be accepted by the researchers with knowledge of and/or interested in the subject of the study.

Self-rated knowledge is not an objective measure to assess respondents' knowledge level. Yet, as the respondents of this survey are all authors of peer-reviewed publications related to gene editing, the chances of including researchers who are not knowledgeable of the study's subject are reduced. As researchers are directly involved in the advancement of knowledge in their scientific fields, it is fair to say that they are among the most qualified professionals to point out future technology developments.

It is expected that researchers invested in gene editing – as well as in any other research field – may have a positive bias regarding the future developments of their research subjects. The degree of optimism may also be positively correlated with the degree of self-rated knowledge, and may vary according to the respondents' professional fields. Experts in business, for example, are expected to show a stronger optimism bias than the experts in academia [53]. In that sense, the respondents of this survey are probably not as optimistic as respondents in other areas. Anyhow, optimism in expert estimates is not unusual [54] and has not stopped the use of experts' opinions to foresee technology developments [55]. Additionally, the expectations for long-range outcomes of technologies are usually more pessimistic than those for short-range [56]. By asking the respondents of this study to consider a ten-year future horizon, concerns regarding experts' optimism are reduced.

Results

1,274 researchers agreed to participate in this survey, corresponding to a response rate of 3.51%. Of those researchers, 3.45% were disqualified for not knowing gene editing. Of the 1,230 qualified respondents, 59.11% declared having good knowledge and 40.89% some

knowledge about gene editing. We obtained 766 (62.30%) completely filled questionnaires, which corresponds to a sample size with a 95% confidence level and a 5% margin of error. According to their email internet protocols, researchers from 76 countries took part in this study (Figure 2). The United States of America had the highest number of respondents (25.8%), followed by Brazil (8.5%), United Kingdom (6.8%), India (5.5%), Italy (4.8%) and Spain (4.2%).

The two-mode network of authors' keywords and Research Areas refers only to the 1,956 publications of the 1,230 qualified respondents (Figure 2). The network shows the authors' keywords with a frequency higher than 14 (network's left side) and the top 10 Research Areas (right side). The orange nodes represent the authors' keywords, and yellow nodes the Research Areas. Blue edges represent the highest co-occurrences in the network. The most central node among the authors' keywords is 'Gene editing' (EG=1.0), followed by 'CRISPR/Cas9' (EG=0.953), 'DNA repair' (EG=0.881), and 'Gene therapy' (EG=0.812). These keywords have co-occurrences with all the Research Areas. The most important connection among authors' keywords is between 'CRISPR/Cas9' and 'Gene editing' as they co-occur in 5.1% of all records, followed by 'CRISPR/Cas9' and 'Cas9' (1.4%). Considering Research Areas, the most central node is 'Biochemistry & Molecular Biology' (EG=1.0), followed by 'Biotechnology & Applied Microbiology' (EG=0.897) and 'Genetics & Heredity' (EG=0.856). The most important connection among Research Areas occurs between 'Biochemistry & Molecular Biology' and 'Chemistry' as they co-occur in 41.9% of all records, followed by 'Biotechnology & Applied Microbiology' and 'Genetics & Heredity' (40.9%). The Research Areas 'Biochemistry & Molecular Biology' and 'Genetics & Heredity' are, respectively, linked to 93.1% and 82.8% of the authors' keywords.

Figure 2 - Global distribution of respondents and network of authors' keywords and Research Areas

Most respondents (70.74%) believe that, in the future, the technological standard will continue to be dependent on double-stranded breaks (DSB) through programmable nucleases (Figure 3). However, this scenario is more likely for researchers with a good level of knowledge - 75.70% versus 63.33% of respondents with some knowledge. Of those who indicated that DSB will be the technological standard, the vast majority (76.30%) believe

that CRISPR-CAS will be the dominant programmable nuclease (Figure 3). There was a statistically significant difference in responses from respondents with good and some knowledge. The belief that CRISPR-CAS will be the dominant programmable nuclease was even stronger among respondents with good knowledge (80.30%). For 15.79% of the respondents, however, we will not have a dominant technological pattern in the future, but rather multiple complementary programmable nucleases.

Figure 3 - Future of programmable nucleases in gene editing

To become viable as an option for disease treatment and prevention in the future, gene editing still needs to overcome several challenges (Figure 4). Immune responses to repeated in vivo administration of vectors were considered important and very important by 40.01% and 20.05% of researchers, respectively. The occurrence of off-targeting mutations was the challenge that presented the highest percentage of very important indications (42.93%). There was, however, a significant statistical difference between the responses of the two groups of respondents (some knowledge and good knowledge). This challenge was considered very important by 46.91% of the researchers with good knowledge and 36.34% of the researchers with some knowledge. Scientific and medical communities' resistance to adopting new technologies was considered a minor challenge and of moderate importance for, respectively, 28.42% and 32.27% of the researchers. Ethical challenges were considered very important and important by, respectively, 47.23% and 29.89% of the researchers. Regulatory challenges were considered very important for 43.49% and important for 36.95% of the respondents.

Figure 4 – Challenges related to the use of gene editing

We used the answers collected in the questions related to the challenges of using gene editing to build a Kendall tau correlation matrix (Supplementary Material). All correlations of these questions were statistically significant. Two groups of challenges with a higher correlation were identified. The first group includes social and institutional challenges (ethical challenges, regulatory challenges, science and medical community resistance, and lack of scientific validation) and the second group includes technological challenges (in vivo targeting, reaching therapeutic levels, off-targeting mutations, and immune responses). Ethical and regulatory challenges have the highest correlation level (0.51). Even though the lack of scientific validation is part of the social and institutional group, it also has a medium

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level correlation with all the other technological challenges. In the second group, in vivo targeting and reaching therapeutic levels are the most correlated questions (0.36), followed by the relationship between in vivo targeting and immune responses from repeated use (0.27).

Figure 5 presents the respondents' expectations on the use of gene editing for the treatment and prevention of human diseases, as well as their applicability and efficacy. The figure is composed of the combination of three graphs, segmented by four groups of diseases: infectious, cancer, hereditary monogenics, and hereditary polygenic. The first graph (upper part) refers to the respondents' level of knowledge on the use of gene editing for disease treatment and prevention. The second and third graphs refer, respectively, to the applicability (lower left quadrant) and efficacy (upper left quadrant) of gene editing, subdivided into treatment and prevention. The respondent will only have access to the questions of applicability and efficacy of treatment and prevention for those types of diseases in which they declared at least having some knowledge. Applicability is understood as the level at which gene editing can be implemented in a distinct context [57]. Effectiveness is understood as the ability of a medical technology to generate expected results under ideal circumstances [58]. In this sense, the greater the applicability of gene editing to treat and prevent diseases, the greater will be its efficacy. To ensure consistency of results, responses indicating that there will be no applicability, but there will be efficacy, or the opposite, that there will be no efficacy, but there will be applicability, were excluded.

The predominant expectation among respondents is that gene editing is likely to have applicability for the prevention of some diseases in each of the four disease groups: infectious (69.09%), cancer (59.35%), hereditary monogenics (48.06%), and hereditary polygenic (35.73%). In the case of applicability for the prevention of infectious diseases, there was a statistically significant difference between the perception of respondents with some and good knowledge - 58.64% of researchers with good knowledge stated that the technology will probably be applied to some infectious diseases, against 73.45% of respondents with some knowledge. Prevention of hereditary monogenic diseases using gene editing achieved the highest percentages of applicability for all diseases (8.66%) and applicability for most diseases (33.73%). On the other hand, gene editing would have lower

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applicability for the prevention of hereditary polygenic diseases, where 3.32% of respondents indicated that it would have applicability for all diseases and 10.80% for most diseases.

As in the case of disease prevention, hereditary polygenic was the disease group with the least applicability for treatment. It was considered not applicable for 31.02% of researchers. For hereditary monogenic diseases, 40.60% of respondents believe gene editing will have applicability for the treatment of most diseases and 7.91% for all diseases. For most respondents, gene editing would be applicable only for the treatment of some cancer (59.01%) and infectious diseases (71.64%).

Consistent with the results on the applicability of gene editing for treatment and prevention of hereditary polygenic diseases, 50.02% of respondents indicated that gene editing will not be effective and 25.76% that it will be effective on average for disease prevention. In terms of efficacy for the treatment of hereditary polygenic diseases, 31.02% of researchers indicated that the gene edition will not be effective and 42.11% that it will have average effectiveness. For the prevention of hereditary monogenic diseases, 34.98% believe that the gene edition will be highly effective and 43.50% that it will have average effectiveness. For treatment, 37.91% believe it will be highly effective and 54.18% believe it will have average effectiveness.

For cancer treatment, 66.84% of respondents believe that gene editing will have average efficacy and 4.93% that it will have low efficacy. For cancer prevention, 16.72% of respondents expect that gene edition will have high efficacy, and 44.20% and 20.65% medium and low efficacy, respectively. For the treatment of infectious diseases, 62.73% of the respondents considered that gene editing will have medium efficacy and 5.64% believe that it will have low efficacy. For the prevention of infectious diseases, 50.27% believe that gene edition will have medium efficacy and 10.56% believe that it will have low efficacy.

Figure 5 – Gene editing for treatment and prevention of diseases

Aside from two questions (applicability to prevent infectious diseases, and efficacy to treat hereditary monogenic diseases), all other questions related to the use of gene editing to treat and prevent diseases are positively correlated – and most have a medium level correlation (above 0.25). In general, all pairs of questions of applicability and efficacy related to the same disease and purpose (treatment or prevention) are highly correlated

(above 0.46). Questions of prevention are more interrelated, especially in the case of hereditary monogenic and polygenic diseases (with an estimated correlation above 0.39), and in the case of cancer and hereditary polygenic diseases (with an estimated correlation above 0.46). Questions of cancer treatment are more related to questions of treatment of infectious diseases (above 0.28). This is also seen in the questions of cancer and infectious disease prevention (above 0.39) (see Supplementary Material for Kendall tau correlation analysis).

Discussion

Most of the researchers who took part in this survey believe that the future of gene editing will still be based on DSB. In scientific literature, few studies are focused on the search for alternatives to DSB for gene edition [59]. In this sense, the preference for DSB expressed by the respondents seems to reflect the focus of research in gene editing, aimed at improving DSB technologies [3,35,38,41]. There are, however, technological alternatives to DSB, such as prime editing [59] and base editing [60,61]. Still in the early stages of development, prime editing and base editing are considered promising for, e.g., reducing the risk of off-targeting mutations, which is the main technological challenge reported by the respondents of this survey. And, for those respondents who believe that DSB will be the main gene editing method in the future, CRISPR was the preferred programmable nuclease. This result may be related to some characteristics of CRISPR, considered the most accessible, cheapest, and easiest to use programmable nuclease [3,4,42]. Anyhow, the belief in the future technological standards is not correlated with the gene editing-related challenges and uses covered in this study. Of the few statistically significant cases, the Cramer's V correlation estimative revealed a very weak correlation between the technological standards questions and all the other questions of the study (0.05 at most). The application of gene editing for the treatment of diseases was the most accepted option by the researchers who participated in this survey. In part, this can be explained by the increased risk of off-targeting involved in embryonic cell gene editing for disease prevention [42]. At odds with part of the literature [13,41], overall, the respondents do not consider that gene editing could become a universal solution for the treatment of any type of disease. This is because it should have different levels of applicability and effectiveness

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for each type of disease. Hereditary monogenic diseases are those that respondents indicated that the use of gene editing will have higher levels of applicability and efficacy. On the other hand, the expectations for the treatment of polygenic hereditary diseases are lower. Polygenic hereditary diseases result from the association between multiple genetic combinations and environmental factors. As such, they are much more difficult to treat or prevent using gene editing technologies [15,62].

In part, overcoming scientific and technological challenges is associated with ethical and regulatory issues [41]. For example, off-targeting mutations in germ cells can be transmitted to future generations [42]. This may raise ethical issues in research, as well as give rise to the establishment of regulatory barriers. Off-targeting mutations are, however, very difficult to identify, imposing major challenges to regulatory activities [4]. This has given rise to important ethical and regulatory debates. There is, however, no consensus in the scientific community on the issue of stem cells. Some as many scientists advocate banning this practice as some advocate regulation [2], and use in humans only when the technology is mature [4]. Many respondents of this study considered off-targeting mutations, regulatory and ethical issues as important or very important challenges for the future of gene editing. The Kendall tau correlation estimative shown that these three questions are correlated, but especially ethical and regulatory challenges (0.51). For its part, the off-targeting mutation was the technological challenge with the highest correlation with ethical challenges (0.15).

Final Remarks

This article presented the results of a global web-based survey of over one thousand gene editing-related researchers. Despite the relevance attributed to ethical and regulatory aspects, the results of this survey suggest that in the next 10 years gene editing may become a reality in the treatment and prevention of a variety of human diseases. Thus, the development and diffusion of the use of gene editing could profoundly change the way medicine, health systems, and public health deal with the treatment and prevention of human diseases. Preparing for the future is therefore not only a necessity for scientists and research organizations working on the development of gene editing, but also for physicians, managers, policymakers, and organizations working in healthcare and public health. Thus, as we seek to anticipate what the next 10 years may bring us, we hope that

the results of this study may foster new studies and discussions, helping these stakeholders to better prepare for the future of the treatment and prevention of human diseases.

Acknowledgments

The authors thank the Center for Strategic Studies of Oswaldo Cruz Foundation for institutional support, the respondents who participated in this study, and Dr Carlos Conte for the review of the statistical analysis. We also thank the reviewers for their valuable comments and suggestions, which have greatly improved this article. The authors received no funding for this work.

Author Disclosure Statement

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Figure legends

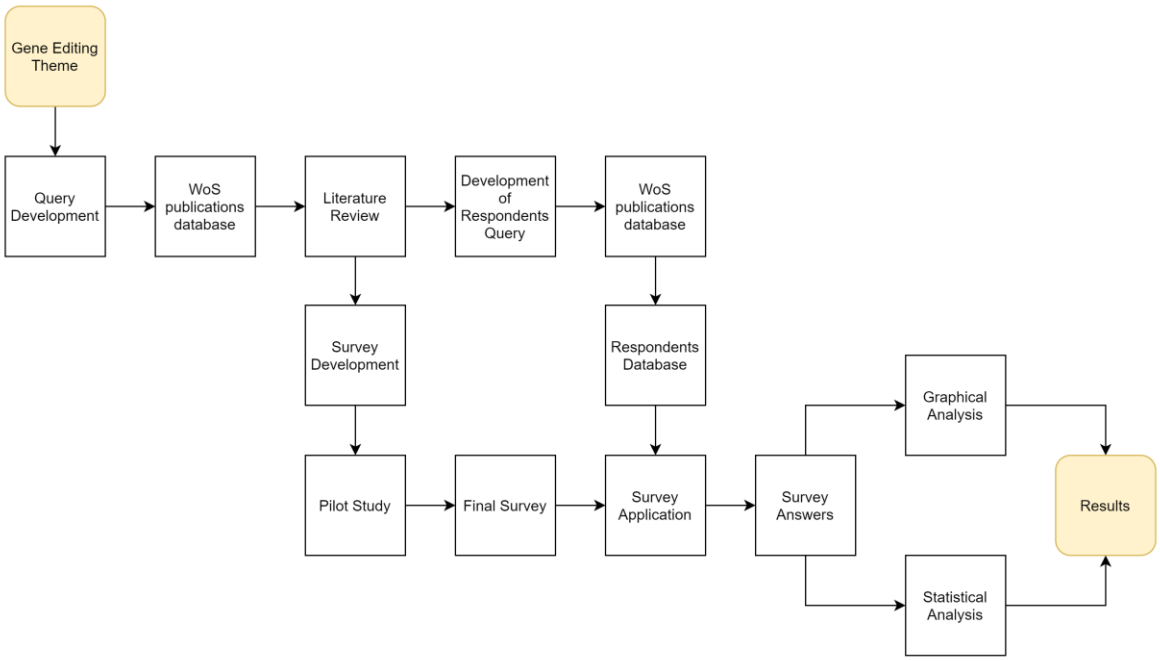

Figure 1 – Methods

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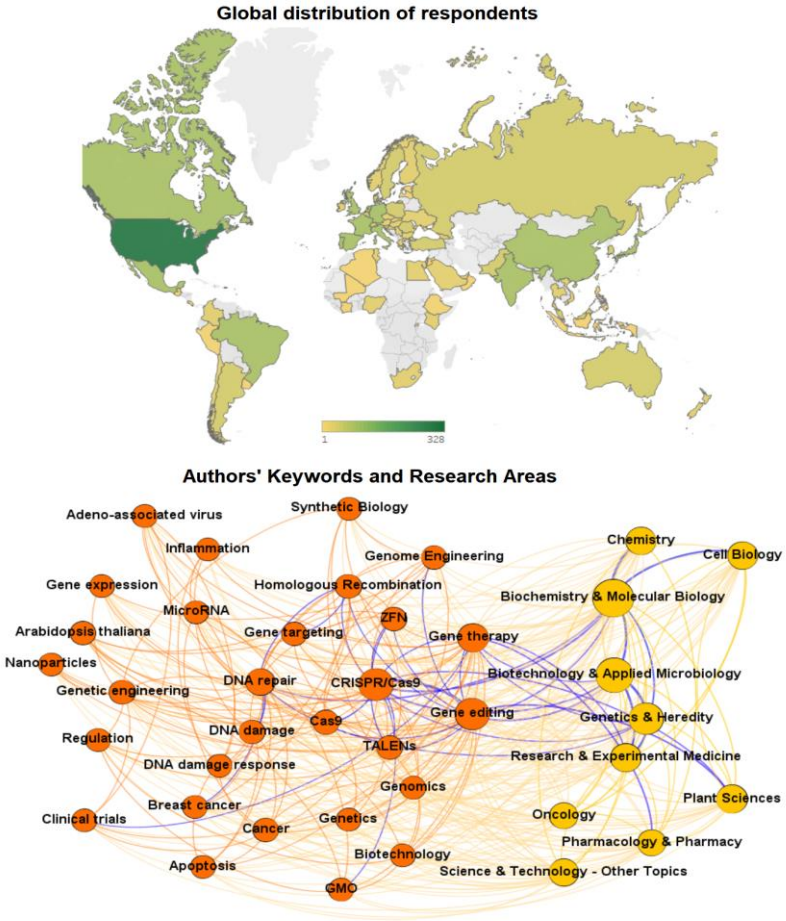

Figure 2 - Global distribution of respondents and network of authors' keywords and Research Areas

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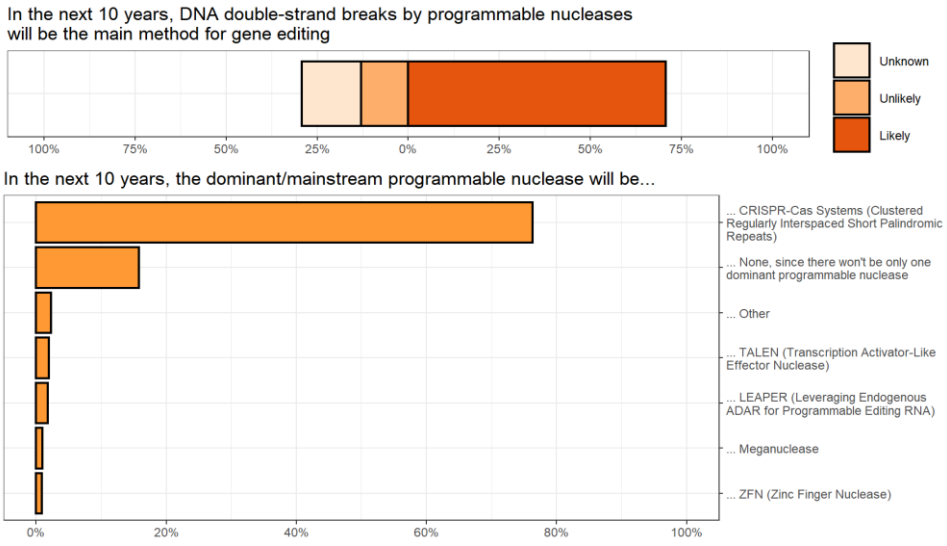

Figure 3 - Future of programmable nucleases in gene editing

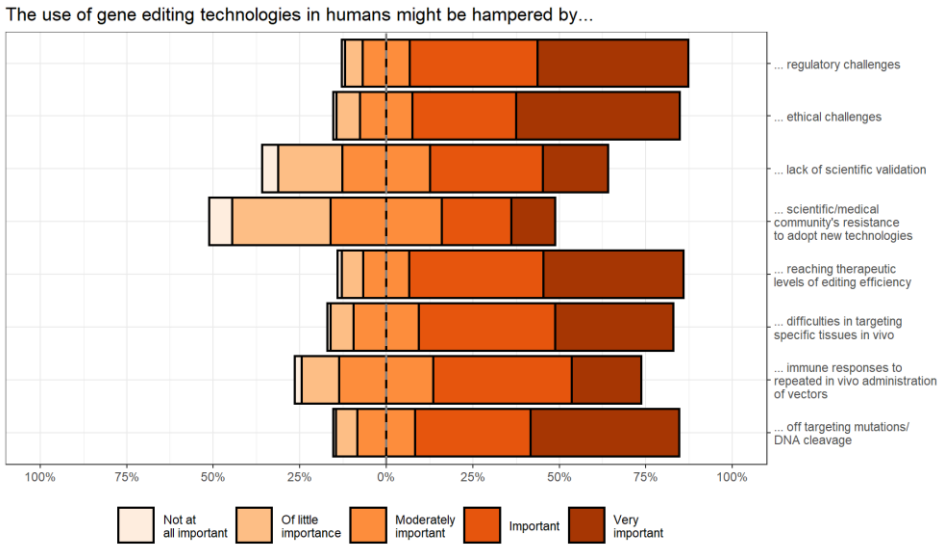

Figure 4 – Challenges related to the use of gene editing

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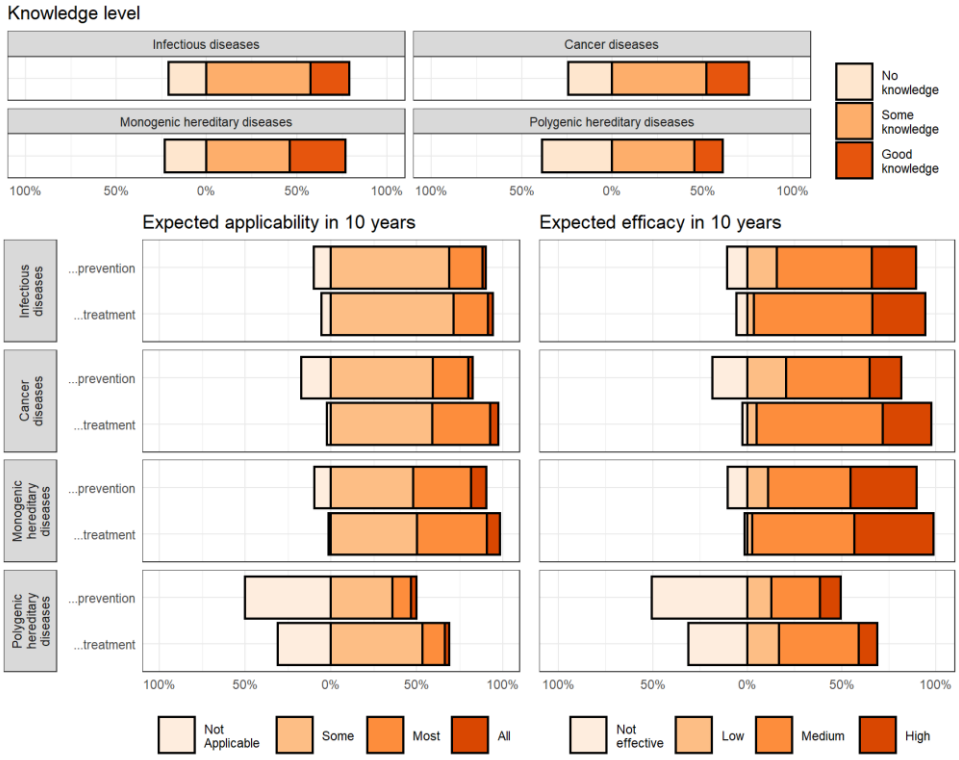

Figure 5 – Gene editing for treatment and prevention of diseases

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Confidence Interval Estimates

Table 1 - In the next 10 years, DNA double-strand breaks by programmable nucleases will be the main method for gene editing

Knowledge	N	Answer	Count	Est	Lower Interval	Upper Interval
Good knowledge	716	Likely	542	75,7%	72,8%	78,9%
Good knowledge	716	Unlikely	96	13,4%	10,5%	16,6%
Good knowledge	716	Unknown	78	10,9%	8,0%	14,1%
Some knowledge	480	Likely	304	63,3%	59,2%	67,9%
Some knowledge	480	Unlikely	59	12,3%	8,1%	16,9%
Some knowledge	480	Unknown	117	24,4%	20,2%	28,9%
Total	1196	Likely	846	70,7%	68,2%	73,4%
Total	1196	Unlikely	155	13,0%	10,5%	15,6%
Total	1196	Unknown	195	16,3%	13,8%	18,9%

Table 2 - In the next 10 years, the dominant/mainstream programmable nuclease will be...

Knowledge	N	Answer	Count	Est.	Lower Interval	Upper Interval
Good knowledge	533	... Other	12	2,3%	0,0%	5,6%
Good knowledge	533	... TALEN (Transcription Activator-Like Effector Nuclease)	4	0,8%	0,0%	4,1%
Good knowledge	533	... ZFN (Zinc Finger Nuclease)	1	0,2%	0,0%	3,5%
Good knowledge	533	... Meganuclease	2	0,4%	0,0%	3,7%
Good knowledge	533	... CRISPR-Cas Systems (Clustered Regularly Interspaced Short Palindromic Repeats)	428	80,3%	77,1%	83,6%
Good knowledge	533	... LEAPER (Leveraging Endogenous ADAR for Programmable Editing RNA)	8	1,5%	0,0%	4,8%
Good knowledge	533	... None, since there won't be only one dominant programmable nuclease	78	14,6%	11,4%	17,9%
Some knowledge	290	... Other	7	2,4%	0,0%	7,9%
Some knowledg	290	... TALEN (Transcription Activator-Like Effector Nuclease)	12	4,1%	0,0%	9,6%

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e						
Some knowledge	290	... ZFN (Zinc Finger Nuclease)	6	2,1%	0,0%	7,6%
Some knowledge	290	... Meganuclease	6	2,1%	0,0%	7,6%
Some knowledge	290	... CRISPR-Cas Systems (Clustered Regularly Interspaced Short Palindromic Repeats)	200	69,0%	64,1%	74,5%
Some knowledge	290	... LEAPER (Leveraging Endogenous ADAR for Programmable Editing RNA)	7	2,4%	0,0%	7,9%
Some knowledge	290	... None, since there won't be only one dominant programmable nuclease	52	17,9%	13,1%	23,4%
Total	823	... Other	19	2,3%	0,0%	5,2%
Total	823	... TALEN (Transcription Activator-Like Effector Nuclease)	16	1,9%	0,0%	4,8%
Total	823	... ZFN (Zinc Finger Nuclease)	7	0,9%	0,0%	3,7%
Total	823	... Meganuclease	8	1,0%	0,0%	3,8%
Total	823	... CRISPR-Cas Systems (Clustered Regularly Interspaced Short Palindromic Repeats)	628	76,3%	73,5%	79,2%
Total	823	... LEAPER (Leveraging Endogenous ADAR for Programmable Editing RNA)	15	1,8%	0,0%	4,7%
Total	82	... None, since there won't be only one	130	15,8	13,0%	18,7%

	3	dominant programmable nuclease		%		

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Table 3 - The use of gene editing technologies in humans might be hampered by...

Comp.	Knowledge	N	Answer	Count	Est.	Lower Interval	Upper Interval
... off targeting mutations/ DNA cleavage	Good knowledge	680	Not at all important	5	0,7%	0,0%	4,7%
... off targeting mutations/ DNA cleavage	Good knowledge	680	Of little importance	39	5,7%	1,8%	9,7%
... off targeting mutations/ DNA cleavage	Good knowledge	680	Moderately important	109	16,0 %	12,1%	20,0%
... off targeting mutations/ DNA cleavage	Good knowledge	680	Important	208	30,6 %	26,6%	34,6%
... off targeting mutations/ DNA cleavage	Good knowledge	680	Very important	319	46,9 %	42,9%	50,9%
... off targeting mutations/ DNA cleavage	Some knowledge	410	Not at all important	4	1,0%	0,0%	6,2%
... off targeting mutations/ DNA cleavage	Some knowledge	410	Of little importance	28	6,8%	1,7%	12,1%
... off targeting mutations/ DNA cleavage	Some knowledge	410	Moderately important	74	18,0 %	12,9%	23,3%
... off targeting mutations/ DNA	Some knowledg	410	Important	155	37,8 %	32,7%	43,0%

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cleavage	e						
... off targeting mutations/ DNA cleavage	Some knowledge	410	Very important	149	36,3 %	31,2%	41,6%
... off targeting mutations/ DNA cleavage	Total	1090	Not at all important	9	0,8%	0,0%	4,1%
... off targeting mutations/ DNA cleavage	Total	1090	Of little importance	67	6,1%	3,0%	9,4%
... off targeting mutations/ DNA cleavage	Total	1090	Moderately important	183	16,8 %	13,7%	20,0%
... off targeting mutations/ DNA cleavage	Total	1090	Important	363	33,3 %	30,2%	36,6%
... off targeting mutations/ DNA cleavage	Total	1090	Very important	468	42,9 %	39,8%	46,2%
... immune responses to repeated in vivo administration of vectors	Good knowledge	675	Not at all important	14	2,1%	0,0%	6,2%
... immune responses to repeated in vivo administration of vectors	Good knowledge	675	Of little importance	89	13,2 %	9,3%	17,3%
... immune responses to repeated in vivo administration of	Good knowledge	675	Moderately important	188	27,9 %	24,0%	32,0%

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vectors							
... immune responses to repeated in vivo administration of vectors	Good knowledge	675	Important	258	38,2 %	34,4%	42,4%
... immune responses to repeated in vivo administration of vectors	Good knowledge	675	Very important	126	18,7 %	14,8%	22,8%
... immune responses to repeated in vivo administration of vectors	Some knowledge	407	Not at all important	7	1,7%	0,0%	7,1%
... immune responses to repeated in vivo administration of vectors	Some knowledge	407	Of little importance	28	6,9%	2,0%	12,3%
... immune responses to repeated in vivo administration of vectors	Some knowledge	407	Moderately important	106	26,0 %	21,1%	31,4%
... immune responses to repeated in vivo administration of vectors	Some knowledge	407	Important	175	43,0 %	38,1%	48,4%
... immune responses to repeated in vivo administration of vectors	Some knowledge	407	Very important	91	22,4 %	17,4%	27,7%
... immune responses	Total	108	Not at all	21	1,9%	0,0%	5,2%

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to repeated in vivo administration of vectors		2	important				
... immune responses to repeated in vivo administration of vectors	Total	1082	Of little importance	117	10,8%	7,7%	14,0%
... immune responses to repeated in vivo administration of vectors	Total	1082	Moderately important	294	27,2%	24,0%	30,4%
... immune responses to repeated in vivo administration of vectors	Total	1082	Important	433	40,0%	36,9%	43,2%
... immune responses to repeated in vivo administration of vectors	Total	1082	Very important	217	20,1%	16,9%	23,3%
... difficulties in targeting specific tissues in vivo	Good knowledge	677	Not at all important	7	1,0%	0,0%	5,1%
... difficulties in targeting specific tissues in vivo	Good knowledge	677	Of little importance	50	7,4%	3,4%	11,5%
... difficulties in targeting specific tissues in vivo	Good knowledge	677	Moderately important	118	17,4%	13,4%	21,5%
... difficulties in targeting specific	Good knowledg	677	Important	256	37,8%	33,8%	41,9%

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tissues in vivo	e						
... difficulties in targeting specific tissues in vivo	Good knowledge	677	Very important	246	36,3 %	32,3%	40,4%
... difficulties in targeting specific tissues in vivo	Some knowledge	410	Not at all important	3	0,7%	0,0%	6,0%
... difficulties in targeting specific tissues in vivo	Some knowledge	410	Of little importance	22	5,4%	0,2%	10,6%
... difficulties in targeting specific tissues in vivo	Some knowledge	410	Moderately important	88	21,5 %	16,3%	26,7%
... difficulties in targeting specific tissues in vivo	Some knowledge	410	Important	172	42,0 %	36,8%	47,2%
... difficulties in targeting specific tissues in vivo	Some knowledge	410	Very important	125	30,5 %	25,4%	35,7%
... difficulties in targeting specific tissues in vivo	Total	1087	Not at all important	10	0,9%	0,0%	4,2%
... difficulties in targeting specific tissues in vivo	Total	1087	Of little importance	72	6,6%	3,5%	9,9%
... difficulties in targeting specific tissues in vivo	Total	1087	Moderately important	206	19,0 %	15,8%	22,2%
... difficulties in targeting specific	Total	1087	Important	428	39,4 %	36,2%	42,7%

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tissues in vivo							
... difficulties in targeting specific tissues in vivo	Total	1087	Very important	371	34,1%	31,0%	37,4%
... reaching therapeutic levels of editing efficiency	Good knowledge	679	Not at all important	5	0,7%	0,0%	4,8%
... reaching therapeutic levels of editing efficiency	Good knowledge	679	Of little importance	41	6,0%	2,1%	10,1%
... reaching therapeutic levels of editing efficiency	Good knowledge	679	Moderately important	84	12,4%	8,4%	16,4%
... reaching therapeutic levels of editing efficiency	Good knowledge	679	Important	256	37,7%	33,7%	41,8%
... reaching therapeutic levels of editing efficiency	Good knowledge	679	Very important	293	43,2%	39,2%	47,2%
... reaching therapeutic levels of editing efficiency	Some knowledge	406	Not at all important	8	2,0%	0,0%	7,4%
... reaching therapeutic levels of editing efficiency	Some knowledge	406	Of little importance	26	6,4%	1,5%	11,8%
... reaching therapeutic levels of editing efficiency	Some knowledge	406	Moderately important	61	15,0%	10,1%	20,4%
... reaching therapeutic levels of	Some knowledg	406	Important	165	40,6%	35,7%	46,1%

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editing efficiency	e						
... reaching therapeutic levels of editing efficiency	Some knowledge	406	Very important	146	36,0 %	31,0%	41,4%
... reaching therapeutic levels of editing efficiency	Total	1085	Not at all important	13	1,2%	0,0%	4,5%
... reaching therapeutic levels of editing efficiency	Total	1085	Of little importance	67	6,2%	3,0%	9,4%
... reaching therapeutic levels of editing efficiency	Total	1085	Moderately important	145	13,4 %	10,2%	16,6%
... reaching therapeutic levels of editing efficiency	Total	1085	Important	421	38,8 %	35,7%	42,1%
... reaching therapeutic levels of editing efficiency	Total	1085	Very important	439	40,5 %	37,3%	43,7%
... scientific/medical community's resistance to adopt new technologies	Good knowledge	667	Not at all important	57	8,5%	4,6%	12,6%
... scientific/medical community's resistance to adopt new technologies	Good knowledge	667	Of little importance	207	31,0 %	27,1%	35,1%
... scientific/medical community's resistance to adopt	Good knowledge	667	Moderately important	208	31,2 %	27,3%	35,2%

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new technologies							
... scientific/medical community's resistance to adopt new technologies	Good knowledge	667	Important	111	16,6 %	12,7%	20,7%
... scientific/medical community's resistance to adopt new technologies	Good knowledge	667	Very important	84	12,6 %	8,7%	16,6%
... scientific/medical community's resistance to adopt new technologies	Some knowledge	399	Not at all important	13	3,3%	0,0%	8,6%
... scientific/medical community's resistance to adopt new technologies	Some knowledge	399	Of little importance	96	24,1 %	19,0%	29,4%
... scientific/medical community's resistance to adopt new technologies	Some knowledge	399	Moderately important	136	34,1 %	29,1%	39,4%
... scientific/medical community's resistance to adopt new technologies	Some knowledge	399	Important	102	25,6 %	20,6%	30,9%
... scientific/medical community's resistance to adopt new technologies	Some knowledge	399	Very important	52	13,0 %	8,0%	18,4%
... scientific/medical	Total	106	Not at all	70	6,6%	3,5%	9,8%

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community's resistance to adopt new technologies		6	important				
... scientific/medical community's resistance to adopt new technologies	Total	1066	Of little importance	303	28,4%	25,3%	31,7%
... scientific/medical community's resistance to adopt new technologies	Total	1066	Moderately important	344	32,3%	29,2%	35,5%
... scientific/medical community's resistance to adopt new technologies	Total	1066	Important	213	20,0%	16,9%	23,2%
... scientific/medical community's resistance to adopt new technologies	Total	1066	Very important	136	12,8%	9,7%	16,0%
... lack of scientific validation	Good knowledge	664	Not at all important	38	5,7%	1,8%	9,8%
... lack of scientific validation	Good knowledge	664	Of little importance	149	22,4%	18,5%	26,5%
... lack of scientific validation	Good knowledge	664	Moderately important	164	24,7%	20,8%	28,8%
... lack of scientific validation	Good knowledg	664	Important	192	28,9%	25,0%	33,0%

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	e						
... lack of scientific validation	Good knowledge	664	Very important	121	18,2 %	14,3%	22,3%
... lack of scientific validation	Some knowledge	402	Not at all important	11	2,7%	0,0%	8,1%
... lack of scientific validation	Some knowledge	402	Of little importance	49	12,2 %	7,2%	17,5%
... lack of scientific validation	Some knowledge	402	Moderately important	106	26,4 %	21,4%	31,7%
... lack of scientific validation	Some knowledge	402	Important	155	38,6 %	33,6%	43,9%
... lack of scientific validation	Some knowledge	402	Very important	81	20,1 %	15,2%	25,5%
... lack of scientific validation	Total	1066	Not at all important	49	4,6%	1,5%	7,8%
... lack of scientific validation	Total	1066	Of little importance	198	18,6 %	15,5%	21,8%
... lack of scientific validation	Total	1066	Moderately important	270	25,3 %	22,2%	28,6%
... lack of scientific validation	Total	1066	Important	347	32,6 %	29,5%	35,8%
... lack of scientific validation	Total	1066	Very important	202	18,9 %	15,9%	22,2%
... ethical challenges	Good	663	Not at all	6	0,9%	0,0%	5,0%

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	knowledge		important				
... ethical challenges	Good knowledge	663	Of little importance	55	8,3%	4,4%	12,4%
... ethical challenges	Good knowledge	663	Moderately important	102	15,4%	11,5%	19,5%
... ethical challenges	Good knowledge	663	Important	189	28,5%	24,6%	32,6%
... ethical challenges	Good knowledge	663	Very important	311	46,9%	43,0%	51,0%
... ethical challenges	Some knowledge	404	Not at all important	3	0,7%	0,0%	6,1%
... ethical challenges	Some knowledge	404	Of little importance	17	4,2%	0,0%	9,5%
... ethical challenges	Some knowledge	404	Moderately important	61	15,1%	10,1%	20,4%
... ethical challenges	Some knowledge	404	Important	130	32,2%	27,2%	37,5%
... ethical challenges	Some knowledge	404	Very important	193	47,8%	42,8%	53,1%
... ethical challenges	Total	106	Not at all	9	0,8%	0,0%	4,1%

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		7	important				
... ethical challenges	Total	1067	Of little importance	72	6,7%	3,7%	10,0%
... ethical challenges	Total	1067	Moderately important	163	15,3%	12,2%	18,5%
... ethical challenges	Total	1067	Important	319	29,9%	26,8%	33,2%
... ethical challenges	Total	1067	Very important	504	47,2%	44,1%	50,5%
... regulatory challenges	Good knowledge	666	Not at all important	5	0,8%	0,0%	4,9%
... regulatory challenges	Good knowledge	666	Of little importance	37	5,6%	1,7%	9,7%
... regulatory challenges	Good knowledge	666	Moderately important	85	12,8%	8,9%	16,9%
... regulatory challenges	Good knowledge	666	Important	240	36,0%	32,1%	40,2%
... regulatory challenges	Good knowledge	666	Very important	299	44,9%	41,0%	49,1%
... regulatory challenges	Some knowledge	403	Not at all important	4	1,0%	0,0%	6,4%
... regulatory challenges	Some knowledge	403	Of little importance	18	4,5%	0,0%	9,9%

... regulatory challenges	Some knowledge	403	Moderately important	60	14,9 %	9,9%	20,3%
... regulatory challenges	Some knowledge	403	Important	155	38,5 %	33,5%	43,9%
... regulatory challenges	Some knowledge	403	Very important	166	41,2 %	36,2%	46,6%
... regulatory challenges	Total	1069	Not at all important	9	0,8%	0,0%	4,1%
... regulatory challenges	Total	1069	Of little importance	55	5,1%	2,0%	8,4%
... regulatory challenges	Total	1069	Moderately important	145	13,6 %	10,4%	16,8%
... regulatory challenges	Total	1069	Important	395	37,0 %	33,8%	40,2%
... regulatory challenges	Total	1069	Very important	465	43,5 %	40,3%	46,7%

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Table 4 - Please indicate your knowledge level on applications of gene editing technologies to the treatment or prevention of...

Comp.	Knowledge	N	Answer	Count	Est.	Lower Interval	Upper Interval
...monogenic hereditary diseases	Good knowledge	644	I have good knowledge	302	46,9%	42,9%	51,1%
...monogenic hereditary diseases	Good knowledge	644	I have some knowledge	247	38,4%	34,3%	42,6%
...monogenic hereditary diseases	Good knowledge	644	I have no knowledge	95	14,8%	10,7%	19,0%
...monogenic hereditary diseases	Some knowledge	396	I have good knowledge	25	6,3%	1,5%	11,5%
...monogenic hereditary diseases	Some knowledge	396	I have some knowledge	231	58,3%	53,5%	63,5%
...monogenic hereditary diseases	Some knowledge	396	I have no knowledge	140	35,4%	30,6%	40,6%
...monogenic hereditary diseases	Total	1040	I have good knowledg	327	31,4%	28,2%	34,8%

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			e				
...monogenic hereditary diseases	Total	1040	I have some knowledge	478	46,0%	42,7%	49,3%
...monogenic hereditary diseases	Total	1040	I have no knowledge	235	22,6%	19,3%	25,9%
...monogenic hereditary diseases	Good knowledge	634	I have good knowledge	158	24,9%	20,8%	29,3%
...polygenic hereditary diseases	Good knowledge	634	I have some knowledge	292	46,1%	42,0%	50,4%
...polygenic hereditary diseases	Good knowledge	634	I have no knowledge	184	29,0%	24,9%	33,4%
...polygenic hereditary diseases	Some knowledge	391	I have good knowledge	5	1,3%	0,0%	6,6%
...polygenic hereditary diseases	Some knowledge	391	I have some knowledge	176	45,0%	40,2%	50,4%
...polygenic hereditary diseases	Some knowledge	391	I have no knowledge	210	53,7%	48,8%	59,1%

...polygenic hereditary diseases	Total	1025	I have good knowledge	163	15,9%	12,7%	19,3%
...polygenic hereditary diseases	Total	1025	I have some knowledge	468	45,7%	42,4%	49,0%
...polygenic hereditary diseases	Total	1025	I have no knowledge	394	38,4%	35,2%	41,8%
...infectious diseases	Good knowledge	671	I have good knowledge	230	34,3%	30,4%	38,4%
...infectious diseases	Good knowledge	671	I have some knowledge	349	52,0%	48,1%	56,1%
...infectious diseases	Good knowledge	671	I have no knowledge	92	13,7%	9,8%	17,8%
...infectious diseases	Some knowledge	405	I have good knowledge	8	2,0%	0,0%	6,9%
...infectious diseases	Some knowledge	405	I have some knowledge	268	66,2%	61,7%	71,1%

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...infectious diseases	Some knowledge	405	I have no knowledge	129	31,9 %	27,4%	36,8%
...infectious diseases	Total	1076	I have good knowledge	238	22,1 %	19,1%	25,2%
...infectious diseases	Total	1076	I have some knowledge	617	57,3 %	54,3%	60,4%
...infectious diseases	Total	1076	I have no knowledge	221	20,5 %	17,5%	23,6%
...cancer	Good knowledge	653	I have good knowledge	227	34,8 %	30,6%	38,9%
...cancer	Good knowledge	653	I have some knowledge	296	45,3 %	41,2%	49,5%
...cancer	Good knowledge	653	I have no knowledge	130	19,9 %	15,8%	24,1%
...cancer	Some knowledge	400	I have good knowledge	23	5,8%	1,0%	10,6%
...cancer	Some knowledge	400	I have	255	63,8	59,0%	68,6%

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			some knowledge		%		
...cancer	Some knowledge	400	I have no knowledge	122	30,5 %	25,8%	35,3%
...cancer	Total	1053	I have good knowledge	250	23,7 %	20,6%	27,0%
...cancer	Total	1053	I have some knowledge	551	52,3 %	49,2%	55,6%
...cancer	Total	1053	I have no knowledge	252	23,9 %	20,8%	27,2%

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Table 5 - Considering the next 10 years, indicate the applicability level of gene editing on...

Comp. 1	Comp. 2	Knowledge	N	Answer	Count	Est.	Lower Interval	Upper Interval
...infectious diseases...	...treatment	Good knowledge	223	Not applicable	10	4,5%	0,0%	10,7%
...infectious diseases...	...treatment	Good knowledge	223	Some diseases	158	70,9%	65,5%	77,0%
...infectious diseases...	...treatment	Good knowledge	223	Most diseases	43	19,3%	13,9%	25,5%
...infectious diseases...	...treatment	Good knowledge	223	All diseases	12	5,4%	0,0%	11,6%
...infectious diseases...	...treatment	Some knowledge	553	Not applicable	21	3,8%	0,9%	7,0%
...infectious diseases...	...treatment	Some knowledge	553	Some diseases	455	82,3%	79,4%	85,5%
...infectious diseases...	...treatment	Some knowledge	553	Most diseases	72	13,0%	10,1%	16,2%
...infectious diseases...	...treatment	Some knowledge	553	All diseases	5	0,9%	0,0%	4,1%
...infectious diseases...	...treatment	Total	776	Not applicab	31	4,0%	1,3%	6,8%

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				le				
...infectious diseases...	...treatment	Total	776	Some diseases	613	79,0%	76,3%	81,8%
...infectious diseases...	...treatment	Total	776	Most diseases	115	14,8%	12,1%	17,7%
...infectious diseases...	...treatment	Total	776	All diseases	17	2,2%	0,0%	5,0%
...infectious diseases...	...prevention	Good knowledge	219	Not applicable	37	16,9%	10,5%	23,4%
...infectious diseases...	...prevention	Good knowledge	219	Some diseases	133	60,7%	54,3%	67,3%
...infectious diseases...	...prevention	Good knowledge	219	Most diseases	42	19,2%	12,8%	25,7%
...infectious diseases...	...prevention	Good knowledge	219	All diseases	7	3,2%	0,0%	9,7%
...infectious diseases...	...prevention	Some knowledge	544	Not applicable	62	11,4%	7,9%	15,1%
...infectious diseases...	...prevention	Some knowledge	544	Some diseases	402	73,9%	70,4%	77,6%
...infectious diseases...	...prevention	Some knowledge	544	Most diseases	75	13,8%	10,3%	17,5%
...infectious diseases...	...prevention	Some knowled	544	All diseases	5	0,9%	0,0%	4,6%

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		ge						
...infectious diseases...	...prevention	Total	763	Not applicable	99	13,0%	9,8%	16,2%
...infectious diseases...	...prevention	Total	763	Some diseases	535	70,1%	67,0%	73,4%
...infectious diseases...	...prevention	Total	763	Most diseases	117	15,3%	12,2%	18,6%
...infectious diseases...	...prevention	Total	763	All diseases	12	1,6%	0,0%	4,8%
...cancer...	...treatment	Good knowledge	179	Not applicable	5	2,8%	0,0%	10,5%
...cancer...	...treatment	Good knowledge	179	Some diseases	98	54,7%	47,5%	62,4%
...cancer...	...treatment	Good knowledge	179	Most diseases	63	35,2%	27,9%	42,9%
...cancer...	...treatment	Good knowledge	179	All diseases	13	7,3%	0,0%	15,0%
...cancer...	...treatment	Some knowledge	375	Not applicable	9	2,4%	0,0%	7,6%
...cancer...	...treatment	Some knowledge	375	Some diseases	233	62,1%	57,3%	67,3%
...cancer...	...treatment	Some knowled	375	Most diseases	119	31,7%	26,9%	36,9%

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		ge						
...cancer...	...treatment	Some knowledge	375	All diseases	14	3,7%	0,0%	8,9%
...cancer...	...treatment	Total	554	Not applicable	14	2,5%	0,0%	6,8%
...cancer...	...treatment	Total	554	Some diseases	331	59,7%	55,6%	64,0%
...cancer...	...treatment	Total	554	Most diseases	182	32,9%	28,7%	37,1%
...cancer...	...treatment	Total	554	All diseases	27	4,9%	0,7%	9,1%
...cancer...	...prevention	Good knowledge	179	Not applicable	44	24,6%	17,3%	32,3%
...cancer...	...prevention	Good knowledge	179	Some diseases	95	53,1%	45,8%	60,8%
...cancer...	...prevention	Good knowledge	179	Most diseases	33	18,4%	11,2%	26,2%
...cancer...	...prevention	Good knowledge	179	All diseases	7	3,9%	0,0%	11,6%
...cancer...	...prevention	Some knowledge	375	Not applicable	51	13,6%	8,8%	18,6%
...cancer...	...prevention	Some knowled	375	Some diseases	236	62,9%	58,1%	67,9%

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		ge						
...cancer...	...prevention	Some knowledge	375	Most diseases	79	21,1%	16,3%	26,1%
...cancer...	...prevention	Some knowledge	375	All diseases	9	2,4%	0,0%	7,4%
...cancer...	...prevention	Total	554	Not applicable	95	17,1%	13,2%	21,5%
...cancer...	...prevention	Total	554	Some diseases	331	59,7%	55,8%	64,1%
...cancer...	...prevention	Total	554	Most diseases	112	20,2%	16,2%	24,5%
...cancer...	...prevention	Total	554	All diseases	16	2,9%	0,0%	7,2%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Not applicable	1	0,4%	0,0%	6,9%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Some diseases	135	49,6%	43,8%	56,2%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Most diseases	111	40,8%	34,9%	47,4%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	All diseases	25	9,2%	3,3%	15,7%
...monogenic hereditary	...treatment	Some knowled	365	Not applicab	8	2,2%	0,0%	7,7%

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diseases...		ge		le				
...monogenic hereditary diseases...	...treatment	Some knowledge	365	Some diseases	183	50,1%	44,9%	55,7%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	Most diseases	148	40,5%	35,3%	46,1%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	All diseases	26	7,1%	1,9%	12,7%
...monogenic hereditary diseases...	...treatment	Total	637	Not applicable	9	1,4%	0,0%	5,5%
...monogenic hereditary diseases...	...treatment	Total	637	Some diseases	318	49,9%	45,8%	54,0%
...monogenic hereditary diseases...	...treatment	Total	637	Most diseases	259	40,7%	36,6%	44,8%
...monogenic hereditary diseases...	...treatment	Total	637	All diseases	51	8,0%	3,9%	12,1%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	Not applicable	35	12,9%	7,0%	19,4%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	Some diseases	127	46,7%	40,8%	53,2%
...monogenic hereditary	...prevention	Good knowled	272	Most diseases	79	29,0%	23,2%	35,5%

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diseases...		ge						
...monogenic hereditary diseases...	...prevention	Good knowledge	272	All diseases	31	11,4%	5,5%	17,9%
...monogenic hereditary diseases...	...prevention	Some knowledge	365	Not applicable	24	6,6%	1,4%	12,1%
...monogenic hereditary diseases...	...prevention	Some knowledge	365	Some diseases	180	49,3%	44,1%	54,9%
...monogenic hereditary diseases...	...prevention	Some knowledge	365	Most diseases	135	37,0%	31,8%	42,5%
...monogenic hereditary diseases...	...prevention	Some knowledge	365	All diseases	26	7,1%	1,9%	12,7%
...monogenic hereditary diseases...	...prevention	Total	637	Not applicable	59	9,3%	5,2%	13,4%
...monogenic hereditary diseases...	...prevention	Total	637	Some diseases	307	48,2%	44,1%	52,3%
...monogenic hereditary diseases...	...prevention	Total	637	Most diseases	214	33,6%	29,5%	37,7%
...monogenic hereditary diseases...	...prevention	Total	637	All diseases	57	8,9%	4,9%	13,1%
...polygenic hereditary	...treatment	Good knowled	100	Not applicab	38	38,0%	28,0%	48,3%

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diseases...		ge		le				
...polygenic hereditary diseases...	...treatment	Good knowledge	100	Some diseases	43	43,0%	33,0%	53,3%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	Most diseases	13	13,0%	3,0%	23,3%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	All diseases	6	6,0%	0,0%	16,3%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	Not applicable	71	29,3%	23,1%	36,0%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	Some diseases	136	56,2%	50,0%	62,8%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	Most diseases	32	13,2%	7,0%	19,8%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	All diseases	3	1,2%	0,0%	7,9%
...polygenic hereditary diseases...	...treatment	Total	342	Not applicable	109	31,9%	26,6%	37,6%
...polygenic hereditary diseases...	...treatment	Total	342	Some diseases	179	52,3%	47,1%	58,1%
...polygenic hereditary	...treatment	Total	342	Most diseases	45	13,2%	7,9%	18,9%

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diseases...								
...polygenic hereditary diseases...	...treatment	Total	342	All diseases	9	2,6%	0,0%	8,4%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Not applicable	61	61,0%	52,0%	70,7%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Some diseases	23	23,0%	14,0%	32,7%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Most diseases	8	8,0%	0,0%	17,7%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	All diseases	8	8,0%	0,0%	17,7%
...polygenic hereditary diseases...	...prevention	Some knowledge	242	Not applicable	110	45,5%	38,8%	52,1%
...polygenic hereditary diseases...	...prevention	Some knowledge	242	Some diseases	99	40,9%	34,3%	47,6%
...polygenic hereditary diseases...	...prevention	Some knowledge	242	Most diseases	29	12,0%	5,4%	18,6%
...polygenic hereditary diseases...	...prevention	Some knowledge	242	All diseases	4	1,7%	0,0%	8,3%
...polygenic hereditary	...prevention	Total	342	Not applicab	171	50,0%	44,7%	55,8%

diseases...				le				
...polygenic hereditary diseases...	...prevention	Total	342	Some diseases	122	35,7%	30,4%	41,5%
...polygenic hereditary diseases...	...prevention	Total	342	Most diseases	37	10,8%	5,6%	16,6%
...polygenic hereditary diseases...	...prevention	Total	342	All diseases	12	3,5%	0,0%	9,3%

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Table 6 - Considering the next 10 years, indicate the effectiveness level of gene editing on...

Comp. 1	Comp. 2	Knowledge	N	Answer	Count	Est.	Lower Interval	Upper Interval
...infectious diseases...	...treatment	Good knowledge	223	Not effective	10	4,5%	0,0%	11,6%
...infectious diseases...	...treatment	Good knowledge	223	Low	60	26,9%	20,2%	34,1%
...infectious diseases...	...treatment	Good knowledge	223	Medium	102	45,7%	39,0%	52,9%
...infectious diseases...	...treatment	Good knowledge	223	High	51	22,9%	16,1%	30,0%
...infectious diseases...	...treatment	Some knowledge	553	Not effective	21	3,8%	0,0%	8,3%
...infectious diseases...	...treatment	Some knowledge	553	Low	160	28,9%	24,6%	33,5%
...infectious diseases...	...treatment	Some knowledge	553	Medium	262	47,4%	43,0%	51,9%
...infectious diseases...	...treatment	Some knowledg	55	High	110	19,9%	15,6%	24,4%

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		e	3					
...infectious diseases...	...treatment	Total	776	Not effective	31	4,0%	0,3%	7,8%
...infectious diseases...	...treatment	Total	776	Low	220	28,4%	24,6%	32,1%
...infectious diseases...	...treatment	Total	776	Medium	364	46,9%	43,2%	50,7%
...infectious diseases...	...treatment	Total	776	High	161	20,7%	17,0%	24,5%
...infectious diseases...	...prevention	Good knowledge	221	Not effective	27	12,2%	5,4%	19,3%
...infectious diseases...	...prevention	Good knowledge	221	Low	61	27,6%	20,8%	34,7%
...infectious diseases...	...prevention	Good knowledge	221	Medium	89	40,3%	33,5%	47,3%
...infectious diseases...	...prevention	Good knowledge	221	High	44	19,9%	13,1%	27,0%
...infectious diseases...	...prevention	Some knowledge	549	Not effective	31	5,6%	1,3%	10,2%
...infectious diseases...	...prevention	Some knowledg	54	Low	174	31,7%	27,3%	36,2%

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		e	9					
...infectious diseases...	...prevention	Some knowledge	549	Medium	249	45,4%	41,0%	49,9%
...infectious diseases...	...prevention	Some knowledge	549	High	95	17,3%	12,9%	21,8%
...infectious diseases...	...prevention	Total	770	Not effective	58	7,5%	3,8%	11,3%
...infectious diseases...	...prevention	Total	770	Low	235	30,5%	26,8%	34,3%
...infectious diseases...	...prevention	Total	770	Medium	338	43,9%	40,1%	47,7%
...infectious diseases...	...prevention	Total	770	High	139	18,1%	14,3%	21,8%
...cancer...	...treatment	Good knowledge	179	Not effective	5	2,8%	0,0%	10,3%
...cancer...	...treatment	Good knowledge	179	Low	11	6,1%	0,0%	13,6%
...cancer...	...treatment	Good knowledge	179	Medium	103	57,5%	50,3%	65,0%
...cancer...	...treatment	Good knowledg	17	High	60	33,5%	26,3%	41,0%

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		e	9					
...cancer...	...treatment	Some knowledge	375	Not effective	9	2,4%	0,0%	7,2%
...cancer...	...treatment	Some knowledge	375	Low	17	4,5%	0,3%	9,3%
...cancer...	...treatment	Some knowledge	375	Medium	268	71,5%	67,2%	76,2%
...cancer...	...treatment	Some knowledge	375	High	81	21,6%	17,3%	26,4%
...cancer...	...treatment	Total	554	Not effective	14	2,5%	0,0%	6,6%
...cancer...	...treatment	Total	554	Low	28	5,1%	1,3%	9,1%
...cancer...	...treatment	Total	554	Medium	371	67,0%	63,2%	71,1%
...cancer...	...treatment	Total	554	High	141	25,5%	21,7%	29,5%
...cancer...	...prevention	Good knowledge	178	Not effective	48	27,0%	19,7%	35,0%
...cancer...	...prevention	Good knowledg	17	Low	31	17,4%	10,1%	25,5%

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		e	8					
...cancer...	...prevention	Good knowledge	178	Medium	70	39,3%	32,0%	47,4%
...cancer...	...prevention	Good knowledge	178	High	29	16,3%	9,0%	24,3%
...cancer...	...prevention	Some knowledge	374	Not effective	52	13,9%	8,8%	19,4%
...cancer...	...prevention	Some knowledge	374	Low	83	22,2%	17,1%	27,6%
...cancer...	...prevention	Some knowledge	374	Medium	174	46,5%	41,4%	52,0%
...cancer...	...prevention	Some knowledge	374	High	65	17,4%	12,3%	22,8%
...cancer...	...prevention	Total	552	Not effective	100	18,1%	13,8%	22,5%
...cancer...	...prevention	Total	552	Low	114	20,7%	16,3%	25,0%
...cancer...	...prevention	Total	552	Medium	244	44,2%	39,9%	48,6%
...cancer...	...prevention	Total	55	High	94	17,0%	12,7%	21,4%

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			2					
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Not effective	1	0,4%	0,0%	6,8%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Low	9	3,3%	0,0%	9,8%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	Medium	129	47,4%	41,5%	53,9%
...monogenic hereditary diseases...	...treatment	Good knowledge	272	High	133	48,9%	43,0%	55,4%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	Not effective	8	2,2%	0,0%	7,6%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	Low	7	1,9%	0,0%	7,3%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	Medium	217	59,5%	54,5%	64,9%
...monogenic hereditary diseases...	...treatment	Some knowledge	365	High	133	36,4%	31,5%	41,9%
...monogenic hereditary diseases...	...treatment	Total	637	Not effective	9	1,4%	0,0%	5,6%
...monogenic hereditary	...treatment	Total	63	Low	16	2,5%	0,0%	6,7%

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diseases...			7					
...monogenic hereditary diseases...	...treatment	Total	637	Medium	346	54,3%	50,4%	58,5%
...monogenic hereditary diseases...	...treatment	Total	637	High	266	41,8%	37,8%	45,9%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	Not effective	37	13,6%	7,4%	19,9%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	Low	35	12,9%	6,6%	19,2%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	Medium	99	36,4%	30,1%	42,7%
...monogenic hereditary diseases...	...prevention	Good knowledge	272	High	101	37,1%	30,9%	43,4%
...monogenic hereditary diseases...	...prevention	Some knowledge	364	Not effective	27	7,4%	2,2%	13,0%
...monogenic hereditary diseases...	...prevention	Some knowledge	364	Low	34	9,3%	4,1%	14,9%
...monogenic hereditary diseases...	...prevention	Some knowledge	364	Medium	179	49,2%	44,0%	54,7%
...monogenic hereditary	...prevention	Some knowledg	36	High	124	34,1%	28,8%	39,6%

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diseases...		e	4					
...monogenic hereditary diseases...	...prevention	Total	636	Not effective	64	10,1%	6,0%	14,2%
...monogenic hereditary diseases...	...prevention	Total	636	Low	69	10,8%	6,8%	15,0%
...monogenic hereditary diseases...	...prevention	Total	636	Medium	278	43,7%	39,6%	47,9%
...monogenic hereditary diseases...	...prevention	Total	636	High	225	35,4%	31,3%	39,6%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	Not effective	38	38,0%	28,0%	48,3%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	Low	20	20,0%	10,0%	30,3%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	Medium	30	30,0%	20,0%	40,3%
...polygenic hereditary diseases...	...treatment	Good knowledge	100	High	12	12,0%	2,0%	22,3%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	Not effective	71	29,3%	23,1%	36,3%
...polygenic hereditary	...treatment	Some knowledg	24	Low	36	14,9%	8,7%	21,8%

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diseases...		e	2					
...polygenic hereditary diseases...	...treatment	Some knowledge	242	Medium	112	46,3%	40,1%	53,2%
...polygenic hereditary diseases...	...treatment	Some knowledge	242	High	23	9,5%	3,3%	16,4%
...polygenic hereditary diseases...	...treatment	Total	342	Not effective	109	31,9%	26,3%	37,5%
...polygenic hereditary diseases...	...treatment	Total	342	Low	56	16,4%	10,8%	22,0%
...polygenic hereditary diseases...	...treatment	Total	342	Medium	142	41,5%	36,0%	47,2%
...polygenic hereditary diseases...	...treatment	Total	342	High	35	10,2%	4,7%	15,9%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Not effective	61	61,0%	52,0%	70,5%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Low	8	8,0%	0,0%	17,5%
...polygenic hereditary diseases...	...prevention	Good knowledge	100	Medium	16	16,0%	7,0%	25,5%
...polygenic hereditary	...prevention	Good knowledg	10	High	15	15,0%	6,0%	24,5%

diseases...		e	0					
...polygenic hereditary diseases...	...prevention	Some knowledge	2 4 2	Not effective	111	45,9 %	39,7%	52,8 %
...polygenic hereditary diseases...	...prevention	Some knowledge	2 4 2	Low	35	14,5 %	8,3 %	21,4 %
...polygenic hereditary diseases...	...prevention	Some knowledge	2 4 2	Medium	73	30,2 %	24,0%	37,1 %
...polygenic hereditary diseases...	...prevention	Some knowledge	2 4 2	High	23	9,5%	3,3 %	16,5 %
...polygenic hereditary diseases...	...prevention	Total	3 4 2	Not effective	172	50,3 %	45,0%	56,0 %
...polygenic hereditary diseases...	...prevention	Total	3 4 2	Low	43	12,6 %	7,3 %	18,2 %
...polygenic hereditary diseases...	...prevention	Total	3 4 2	Medium	89	26,0 %	20,8%	31,7 %
...polygenic hereditary diseases...	...prevention	Total	3 4 2	High	38	11,1 %	5,8 %	16,8 %

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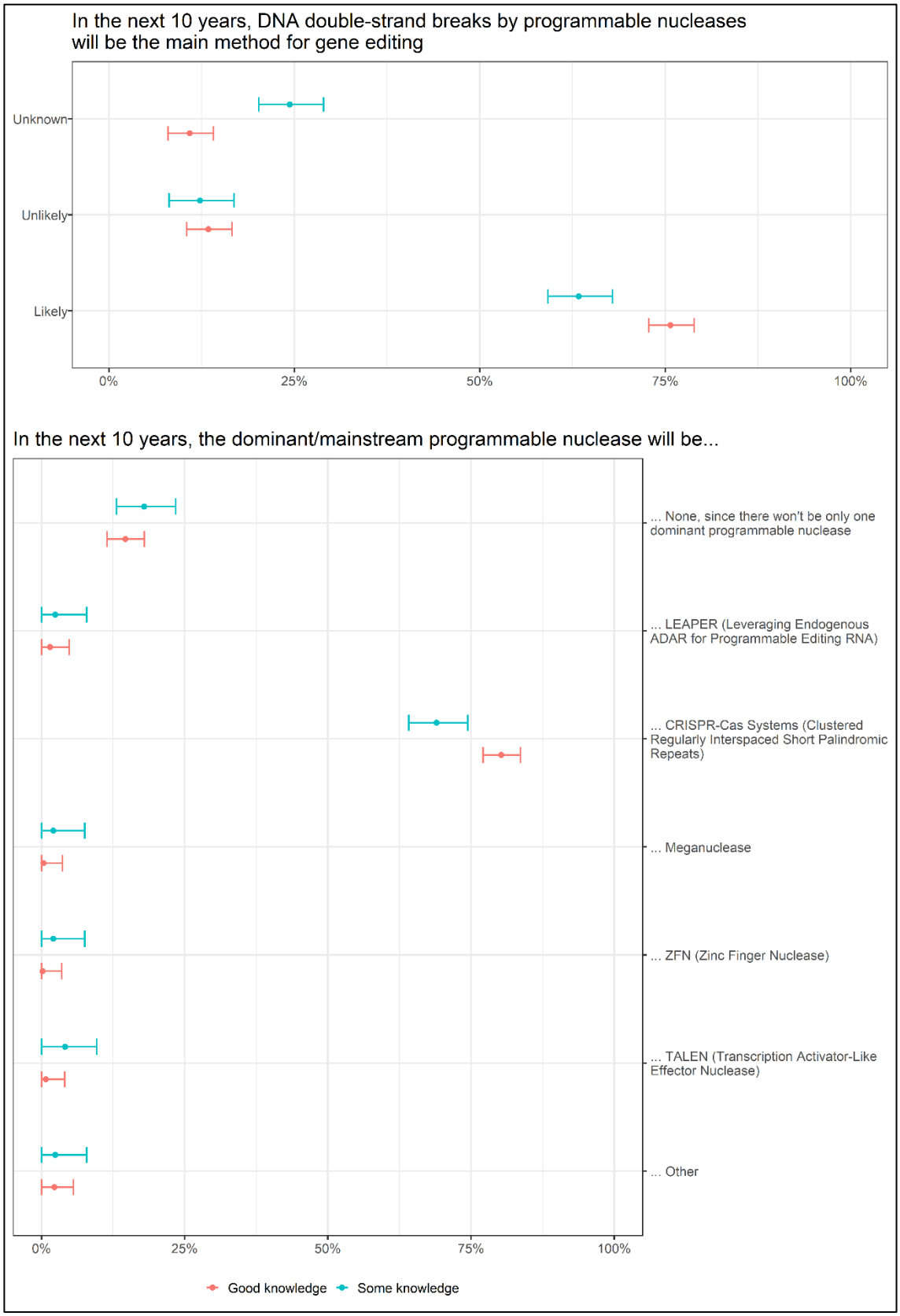

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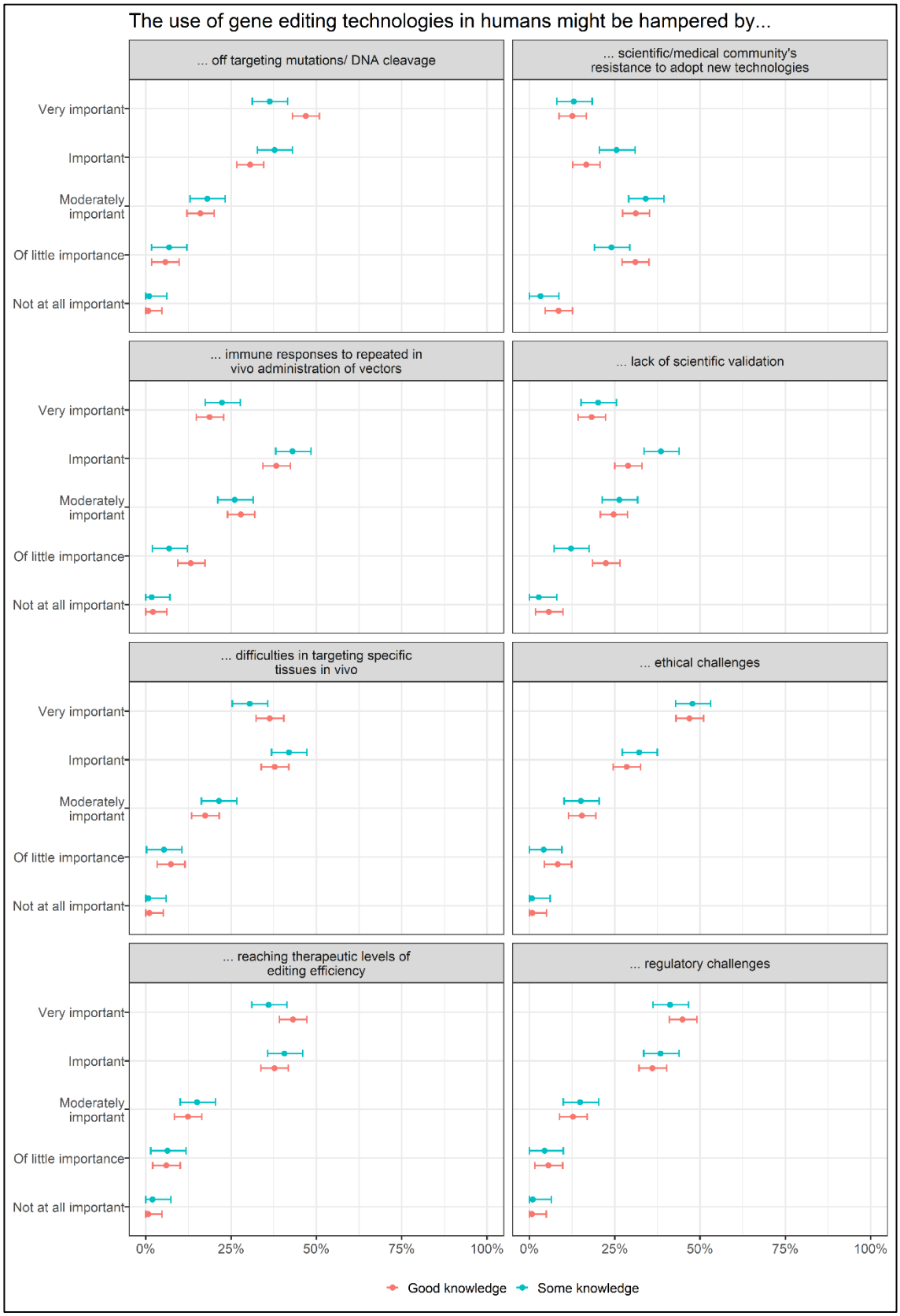

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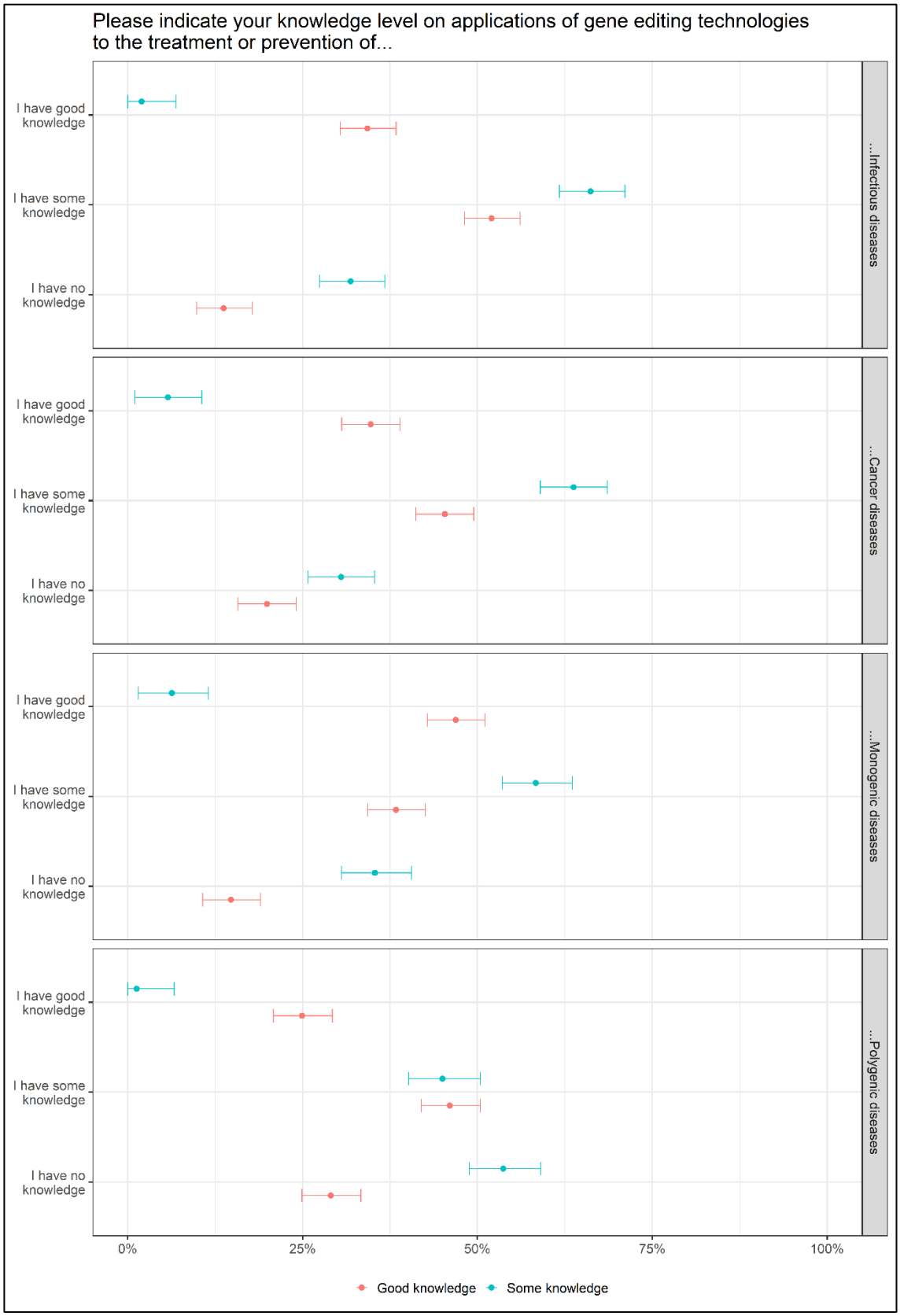

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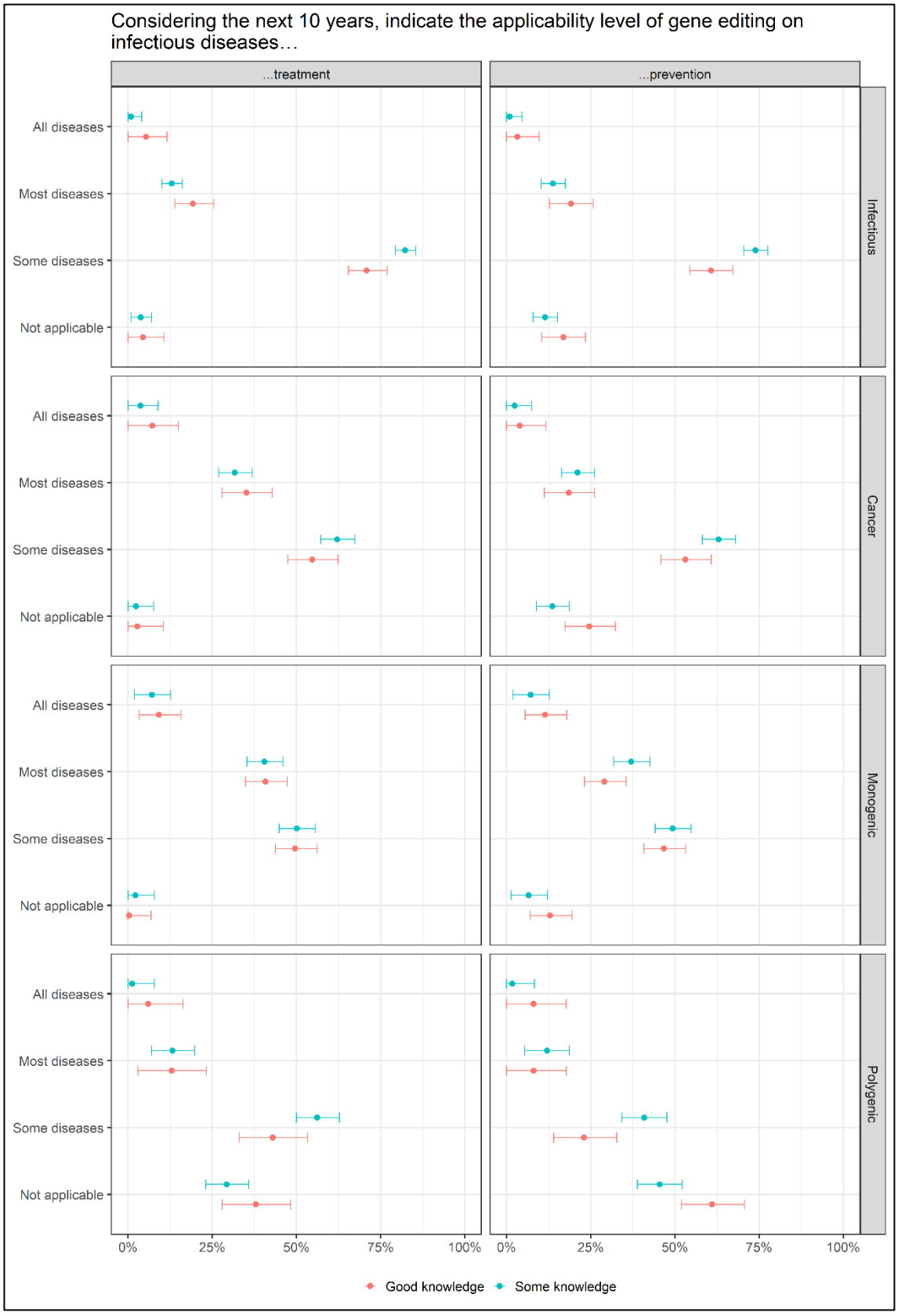

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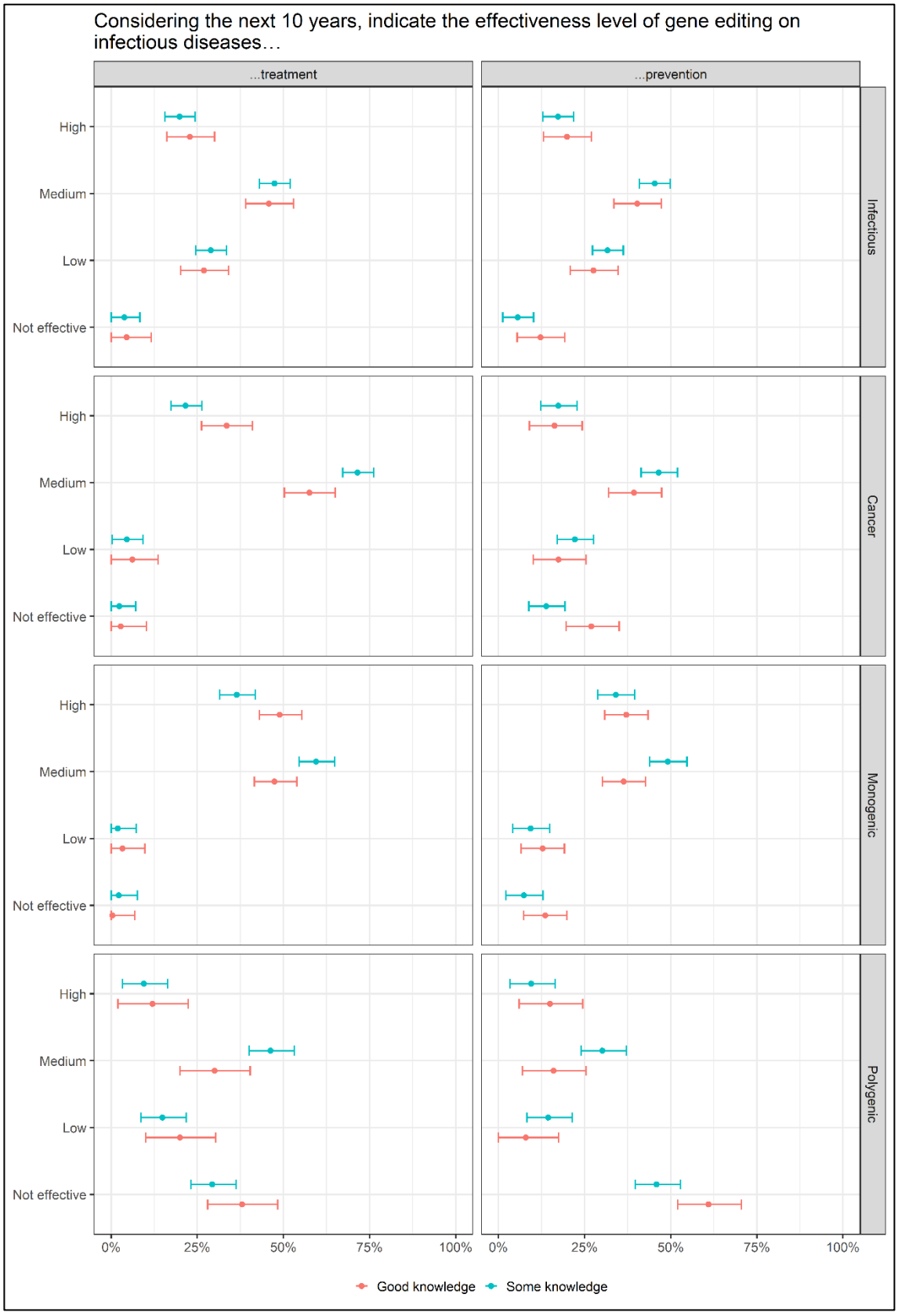

correlation estimates

Table 7 - Correlation estimates between technological standard questions and challenges and usage questions

Q1	Q2	Option	chi	cramerV
DSB based	Challenge	Off-targeting mutations	0,159	-
DSB based	Challenge	Immune responses from repeated use	0,539	-
DSB based	Challenge	In vivo targeting	0,057	0,004
DSB based	Challenge	Reaching therapeutic levels	0,160	-
DSB based	Challenge	Sci./Med. community resistance	0,002	0,052
DSB based	Challenge	Lack of scientific validation	0,094	-
DSB based	Challenge	Ethical challenges	0,187	-
DSB based	Challenge	Regulatory challenges	0,667	-
DSB based	Diseases	Applicability on infectious treatment	0,101	-
DSB based	Diseases	Applicability on infectious prevention	0,538	-
DSB based	Diseases	Effectiveness on infectious treatment	0,645	-
DSB based	Diseases	Effectiveness on infectious prevention	0,950	-
DSB based	Diseases	Applicability on cancer treatment	0,347	-

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DSB based	Diseases	Applicability on cancer prevention	0,306	-
DSB based	Diseases	Effectiveness on cancer treatment	0,027	0,024
DSB based	Diseases	Effectiveness on cancer prevention	0,843	-
DSB based	Diseases	Applicability on monogenic treatment	0,377	-
DSB based	Diseases	Applicability on monogenic prevention	0,029	0,023
DSB based	Diseases	Effectiveness on monogenic treatment	0,284	-
DSB based	Diseases	Effectiveness on monogenic prevention	0,512	-
DSB based	Diseases	Applicability on polygenic treatment	0,175	-
DSB based	Diseases	Applicability on polygenic prevention	0,271	-
DSB based	Diseases	Effectiveness on polygenic treatment	0,001	0,053
DSB based	Diseases	Effectiveness on polygenic prevention	0,016	0,031
Nuclease	Challenge	Off-targeting mutations	0,028	0,040
Nuclease	Challenge	Immune responses from repeated use	0,948	-
Nuclease	Challenge	In vivo targeting	0,072	0,025
Nuclease	Challenge	Reaching therapeutic levels	0,687	-

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Nuclease	Challenge	Sci./Med. community resistance	0,804	-
Nuclease	Challenge	Lack of scientific validation	0,572	-
Nuclease	Challenge	Ethical challenges	0,847	-
Nuclease	Challenge	Regulatory challenges	0,115	0,014
Nuclease	Diseases	Applicability on infectious treatment	0,078	0,014
Nuclease	Diseases	Applicability on infectious prevention	0,060	0,024
Nuclease	Diseases	Effectiveness on infectious treatment	0,049	0,018
Nuclease	Diseases	Effectiveness on infectious prevention	0,221	-
Nuclease	Diseases	Applicability on cancer treatment	0,457	-
Nuclease	Diseases	Applicability on cancer prevention	0,150	-
Nuclease	Diseases	Effectiveness on cancer treatment	0,021	0,046
Nuclease	Diseases	Effectiveness on cancer prevention	0,097	-
Nuclease	Diseases	Applicability on monogenic treatment	0,134	-
Nuclease	Diseases	Applicability on monogenic prevention	0,845	-
Nuclease	Diseases	Effectiveness on monogenic treatment	0,530	-

Nuclease	Diseases	Effectiveness on monogenic prevention	0,592	-
Nuclease	Diseases	Applicability on polygenic treatment	0,200	-
Nuclease	Diseases	Applicability on polygenic prevention	0,125	-
Nuclease	Diseases	Effectiveness on polygenic treatment	0,563	-
Nuclease	Diseases	Effectiveness on polygenic prevention	0,354	-

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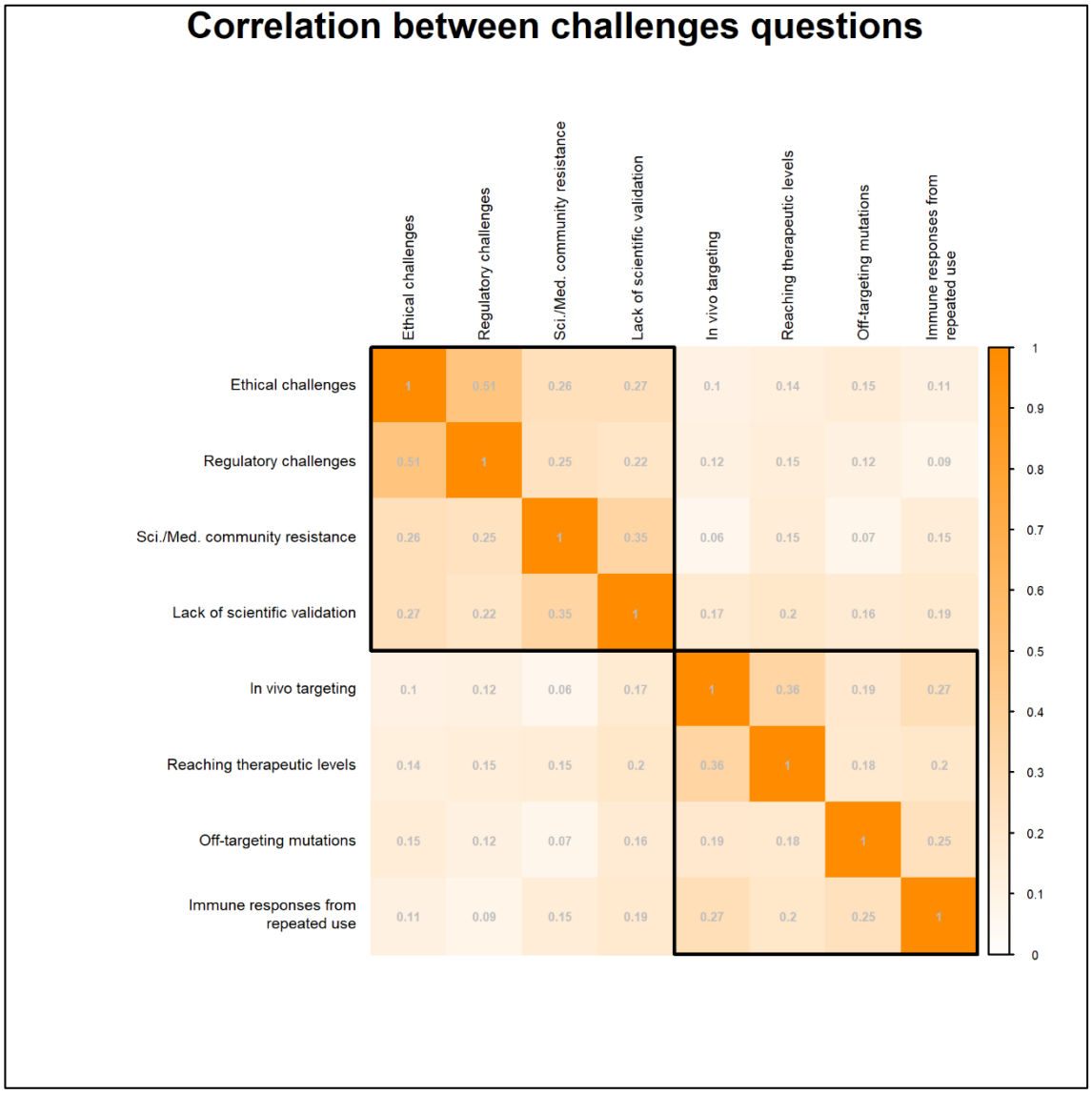

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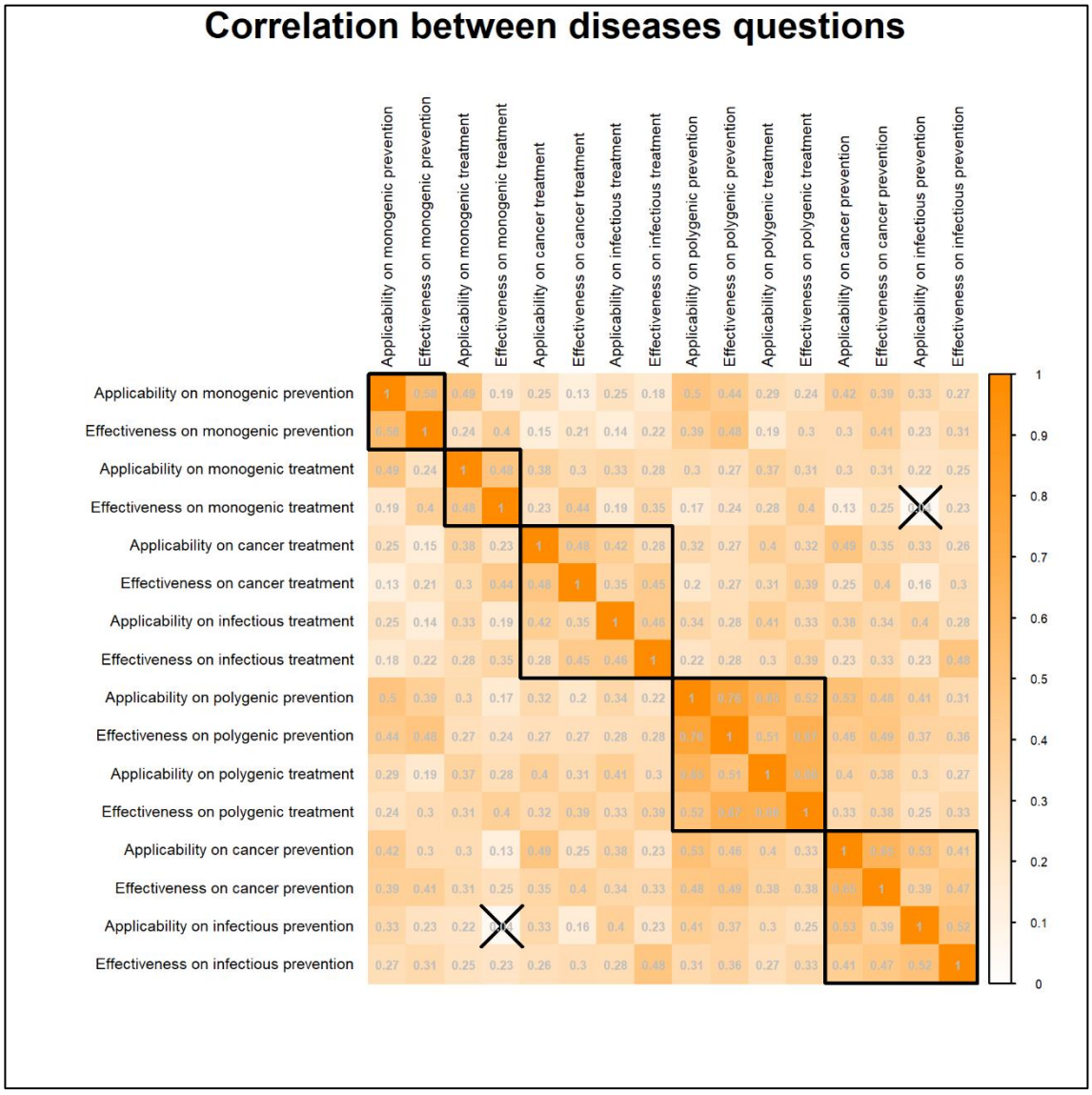

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