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ORIGINAL RESEARCH PAPER

From Asilomar to Genome Editing: Research Ethics and Models of Decision

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Abstract The aim of the presentation is to focus on the differences between two scientific contexts: the genetic engineering context of the 1970s, with specific attention paid to the use of the recombinant DNA technique to generate genetically modified molecules, and the current genome editing context, with specific attention paid to the use of CRISPR-Cas9 technology to modify human germ line cells genetically. In both events, scientists have been involved in discussions that have gone beyond mere professional deontology touching on specific policy issues such as freedom of research, responsibility for the consequences of research, the right of the public to participate in the evaluation of the goals of research methods, the relationship between cost and benefit and possible social consequences. The comparison between these two scientific contexts suggests the need of handling such issues by defining procedures that meet the criteria of democracy and responsibility towards society. The underlying objective should be to effectively launch actions and interventions based not on a hierarchical approach but rather a reticular conception of knowledge.

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Introduction

In recent decades, scientists have developed a series of new experimental approaches. Some of them have challenged the commonly accepted boundaries between human and animal life, and others those between the concepts of the natural and the artificial, reducing the pre-existing limit between reparation and recreation of biological life. In particular, right from the very outset, technical advances in the field of genetic engineering have given rise to substantial controversies and debates. These debates have involved many parts of the scientific community, not to mention bioethicists, politicians and, last but not the least, the public opinion. The focus of these discussions, triggered by surprising experimental advances, concerns the ability of contemporary biology and in particular biotechnology to go beyond the traditional acquisition of knowledge concerning the functioning of living systems. In fact, through genetic engineering, it is possible to interfere systematically with the genetic component of biological life, to modify the information of DNA and to change the development programs it controls, making us creators of ourselves and of other organisms. This growing capacity for intervention is today possible through the use of extremely powerful and refined technical means such as the CRISPR-Cas9

system. Since the first Asilomar conference in 1973, scientists have increasingly become involved in discussions regarding the right to freedom of research, responsibility for the consequences of research, the limitations between basic research and applications, the right of the public to participate in the evaluation of the aims and methods of research, the relationship between cost and benefit and possible social consequences, and on the growing influence of industry in biological research. These represent a real block of political problems that researchers at the beginning had not in the least expected, which are at the center of the current reflection concerning the relationship between science and society. The need for a theoretical background has gradually become clearer through a concerted effort and active collaboration between experts of different cultural and professional backgrounds and an unprecedented convergence between experts and public opinion, all aspects that are at the center of the debate generated in recent years from the use of *genome editing* on human germ line cells.

The central purpose of this work, when life itself is in all its essence becoming an experiment, is to reflect on how doing science necessarily involves questions about the meaning of both human life and the value of scientific knowledge. The feelings of fear and opposition that some experimental practices can provoke require a motivated and exhaustive ethical-political analysis, carefully weighing the risks and opportunities of scientific progress. The underlying objective should be to effectively launch actions and interventions based not on a hierarchical approach but rather a reticular conception of knowledge, namely shifting from a top-down model of knowledge towards a form of public debate and a co-production model. In the first model, science is seen as universal and objective knowledge which is the opposite of lay knowledge. Therefore, science is considered as separate from society, and the public does not intervene in the process of knowledge creation. In the second model, science is seen as incomplete and deficient knowledge without the observations and local knowledge of lay people. Thus, science has to be opened up to debate with citizens to create the necessary conditions for it to be enriched. In the third and more extreme model, science is seen as closely intertwined with society. As a consequence, citizens and concerned groups get involved in the process of knowledge production and of its direct use. Knowledge created in laboratories is still crucial, but "it is framed, and fed by the actions of lay people and by the flow of knowledge and questions they formulate" [1, p. 91].

Recombinant DNA and the Asilomar Conference (1975)

During a conference held at Cold Spring Harbor in the USA in 1971, the researcher, Janet Mertz, announced that a project involving the chromosome of a monkey virus was to be carried out in the laboratory of Paul Berg (Nobel Prize in Chemistry in 1980 along with Walter Gilbert and Frederick Sanger) at Stanford, where she worked. This chromosome was known as SV40 and was to be inserted within the genome of another virus that normally infects and reproduces in the E. coli bacterium cell. This announcement caused a great stir because it was well known that SV40 had the ability to transform normal cells raised in the laboratory into their corresponding tumor type. In short, this bacterium, a common host of the human intestine, would in this way have become the instrument of propagation of a virus known to induce a malignant transformation in normal cells [2]. The fact that this bacterium, once it had accidentally penetrated inside the human intestine, could exchange genetic information with the normal bacterial flora present in the intestine, naturally seemed somewhat unpredictably to increase the chances of risk for the human host. The reactions to the announcement of this experiment were various and controversial. What remains certain, however, was that the possibility of recombining genetic heritages that are so different and biologically distant was received with embarrassed interest by the scientific community. Soon the differences of opinion and the real need for an assessment of the objective risks involved in experimentation based on genetic recombination techniques stimulated a wide debate within the scientific community. The opinions of some researchers, who appeared in an article by Nicholas Wade published in *Science* in November 1973, seemed to summarize the uncertainties and worries circulating in that period [3, 4]. For example, Wade quotes the oncologist Robert Pollack, of Cold Spring Harbor Laboratory, who declared: "It would be a real Disaster if one of the agents now being handled in research should in fact be a Real human cancer agent." ([4], p. 567). In the same article, there is a consideration of the virologist John Todaro who stated that "It's entirely a guess as to risk, but my guess is that it is

considerably less dangerous than smoking two packs of cigarettes a day." ([3], p. 567).

The first conference on the potential biological risks deriving from the application of recombinant DNA technology was held in the winter of 1973 in Asilomar in an old abandoned chapel in the Californian forests near the Ocean, which had been reconverted into a conference center. The echo of this conference never reached the public and was virtually ignored by the popular press. In fact, the only existing scientific document of the conference is a book for specialists entitled "Biohazards in Biological Research" [5]. In June of that same year, however, another scientific conference was held in the USA, the Gordon Conference on Nucleic Acids, in which the results of new research were reported. This study regarded techniques which made the genetic recombination of DNA coming from different species even easier. In fact, the cohesive ends generated after the cut of the DNA with restriction enzymes were discovered: these could easily be used to weld together fragments of DNA of any origin. The reaction to the announcement of these studies was lively and resulted in a letter addressed to the president of the National Academy of American Sciences in which serious concerns were expressed regarding the implications of this research [6]: Maxine Singer and Dieter Soll, the authors of the letter sent to *Science*, expressed all their perplexities in a significant part of this missive: "Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered" ([6], p. 1114). About a month later, a letter was published simultaneously in *Science* and *Nature*, in which the first signee was Paul Berg the creator of the Stanford experiment [7]. In this document, known as "Berg's moratorium," a first assessment of the implicit risk in recombinant DNA technology was made. Two fundamental types of experiments were also outlined, which would have to be renounced by experimenters spontaneously, until the danger deriving from the release of recombinant molecules or organisms carrying them into the environment had been ascertained. The first type of experiment to be avoided consisted in the transformation of bacteria with recombinant molecules that could give rise to bacterial populations resistant to antibiotics or that carry the genetic information necessary for the production of toxins. The second type of experiments to be banned regarded the production of recombinant molecules carrying DNA from tumor viruses, as it was not possible to evaluate the consequences of the propagation of such potentially carcinogenic DNA in humans.

Singer and Soll's letter and the "Berg moratorium" achieved two objectives. The first was to make scientists aware of the potential danger inherent in certain laboratory methods, while the second was to introduce the concept of "containment" of biological risk. A further consequence of the publication of these letters was to generate interest in the popular press: the debate on recombinant DNA was no longer a matter that concerned insiders only.

In his letter, Berg also suggested organizing an international conference in which issues related to potential risks could be discussed, as well as examining the benefits deriving from new recombinant DNA technologies. Berg's proposal was accepted and the congress was held again in Asilomar in 1975, with the participation of 140 researchers, who represented almost all the scientists involved in this type of research across the globe.

In June 1975, following the conclusion of the Asilomar Conference, a special commission (presided by Paul Berg) established a statute (Summary Statement of the Asilomar on Recombinant DNA Molecules) that outlined the objectives and conclusions of the conference [8].

Objectives of the Asilomar Conference:

- "Discuss the most suitable ways to deal with potential biological risks";
- Analyze the «many questions» that the new techniques pose, and establish guidelines to ensure that "scientific work can be undertaken with minimum risks for workers in laboratories, for citizens in general, and for the animal and plant species that share our ecosystem"

Guidelines established to reduce biological risks:

- Biological barriers: use of organisms unable to survive outside the laboratory;
- Physical containment of risk through the physical isolation of the laboratory and the use of appropriate clothing by researchers;
- Education and training of personnel involved in experiments regarding safety measures;
- Responsibility of researchers and companies in experimentation and an invitation to suspend or abandon those experiments that are so dangerous they cannot be contained by safety measures;

- Study of more effective measures in parallel with the development of scientific knowledge

In the objectives and conclusions of the second Asilomar conference, two different sensations are evident among scientists who were interested in the new field of DNA recombination. The first mirrors that expressed by physicists at the time of the discovery of nuclear fission. Biologists, as well as physicists, sensed the potential offered by the new technology without being able to fully assess any accompanying risks. The second sensation had more directly cultural and political connotations. In fact we must not forget that the first pioneering techniques of recombinant DNA came to the fore in the USA at a time when the country was involved in the war in Vietnam and in the years when environmentalist movements started to grow and spread. It was therefore of the utmost importance that this innovative research should not be demonized and this meant that the scientists themselves had to produce the rules and measures to guarantee that they did not lose both the public's trust in scientific research and the fundamental funding required to continue the research. These are some of the reasons why, after the second Asilomar conference, the National Institutes of Health defined the standard laboratory conditions in which the recombination experiments had to be performed [9].

The definition of these general directives by the NIH had an immediate echo even outside the USA. Most researchers who had adopted genetic engineering techniques essentially reacted in two different ways. Some laboratories stopped their work and even went so far as to destroy the bacterial populations that housed recombinant DNA molecules. In other laboratories, on the other hand, the research proceeded without respecting the directives produces by the NIH. In any case, within a couple of years, the same scientists who had previously advocated the need to suspend or even prohibit this kind of experiments found themselves requiring a revision of the rules defined by the NIH. In 1977, Paul Berg, who, as we have seen, had been the main proponent of the moratorium, believed that the time had come to revise such restrictive legislation [10]. Berg maintained that between 1974 and 1977, several lines of research based on genetic engineering had been created. From the results, it was not possible to ascertain the existence of any risk. However, it was instead possible to demonstrate that the *E. coli* strains normally used for genetic engineering experiments were not able to reproduce outside the laboratories. Berg also claimed that, in fact, the genetic engineering experiments performed in the laboratory were nothing but a replication of the phenomena of "natural" recombination. It was therefore reasonable to infer that such experimental systems could not create monsters [11].

After the second conference of Asilomar, the news regarding the possibility of "manipulating" the genetic make-up of an organism and the debate concerning potential risks reached the ears of the public. Moreover, one of the most interesting reports on the conference was realized by Michael Roger for the Rolling Stone magazine [12], the non-specialized press talked of the "creation of life" and manipulation beyond the limits of traditionally-conceived species, thus contributing to the construction of Frankenstein metaphors which, even today, define a large part of the debate concerning these issues [13].

In a very short time, a real cultural revolution occurred in the world of biological research, in which a frightened and worried reaction emerged both from the general public and from many scientists [14]. It was as if with the discovery of genetic engineering, a real sense of loss had taken place within the biological sciences community. In fact, traditional biology was originally a science based on observation, while with the advent of genetic engineering, DNA is separated from its living and real biological environment, with its "manipulation" taking place inside a laboratory container. However, once this molecule is reintroduced into a living cell, it regains all its biological potential. This was the cultural revolution we were referring to and which reflects the complexity of biological research which, unlike physics and chemistry, had no tradition of a direct relationship with the technological application. At the same time, with recombinant DNA and with Asilomar, the need for a different moral responsibility of scientists and governance concerning the relationship between science and society began to grow. As Heather E. Douglas highlighted, Asilomar is a standard example where scientists began to take into consideration the potential harmful consequences of their work beyond the realm of the science (i.e., the non-epistemic consequences of scientific choices), expanding the scientists' responsibility from research integrity towards society [15]. However, from our point of view, this extension of responsibility started with Asilomar, although a key fundamental element in the history of the ethics of research and governance of science, carried on to be embedded in a top-down model of decision-making. Hence, political issues related to possible risks other than biological ones

were not been foreseen. As Sheila Jasanoff pointed out, among "the features that stand out in hindsight, perhaps the most significant is the Asilomar scientist' preoccupation with 'recombinant DNA molecules.' Understandably, given the disciplinare identities of the leading participants, it was the process of altering molecules that garnered the most attention. […] Molecules were small and relatively easy to understand, as well as inanimate, and thus safely removed from question of politics or values. That biotechnology might one day destabilize basic elements of social order - kinship, for example, or farmer' rights to own and sow seeds - was very far from the thought of the field's founding father" ([16], p. 47).

As a consequence, Asilomar's discussion and conclusions excluded a range of ethical-social issues and concerns that were reflected in the inability to consider the possibility of developing policies for inclusion of non-experts capable of going beyond a hierarchical concept of knowledge and creating a sufficient level of cohesion between scientists and citizens around the use of biotechnology. At the same time, in a very short period, "biotechnologies inexorably passed from isolated scientific laboratories to market competition" ([16], p. 48), and these changes made the post-Asilomar assets very fragile, so that they could not remain unchanged considering such a rapidly evolving framework.

2015: CRISPR-Cas9 Technology and Human Genome Editing

Ever since 2015, following a study carried out by a group of Chinese scientists who applied the CRISPR-Cas9 genome engineering technology to human embryos [17], there has been an urgent need for deep dialogue concerning the responsible use of genome editing in the human germline.

In January 2015, American life scientists and experts in ethics and law convened in Napa (California) to discuss the scientific, medical, legal and ethical implications of human germline engineering [18]. This group, including David Baltimore and Paul Berg, called for a more open dialogue on the subject "by a broad cohort of scientists, clinicians, social scientists, the general public, and relevant public entities and interest groups" and made general recommendations about steps to guarantee that any human genome modification is carried out safely and ethically. For instance, they discouraged "any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations" ([18], p. 37).

In May 2015, the US National Academy of Sciences and National Academy of Medicine announced to hold an international summit in the end of 2015 to meet researchers and other experts in order to explore the scientific, ethical, legal, and policy issues associated with human genome editing research.

The Napa group and the National Academies considered their meeting at the light of the Asilomar approach to discuss guidelines and self-regulation for biotechnological developments and accept responsibility for the outcomes of scientific research [19]. Indeed, the Asilomar Conference on Recombinant DNA represents the paradigm model of scientific self-regulation in biosciences, as discussed above, illustrating "how the scientific community can effectively impose a moratorium on certain types of experiments and how a process of self-regulation in science can lead to guidelines for the safe handling of new biotechnologies" ([19], p. 355).

Yet some scholars argued that the self-regulation paradigm originated by Asilomar is inadequate in handling the complexity of human genome editing technologies [20–24]. As we have seen, the Asilomar conference focused strictly on technical issues related to biological risk assessment. The scientists were the subjects involved in this evaluation, and they, after making a peer comparison, disclosed to the public their concerns and recommendations which emerged during the conference. Restricting the assessment to biological risk made it possible to give priority to scientists in the decision-making process, excluding the point of view of the other stakeholders, including the public, so it was considered sufficient to follow the principles of transparency and openness in their relationship with the public, without taking into account active forms of involvement.

In the context of human genome editing, risk assessment is no longer a strictly technical assessment but involves policy issues. This is a decisive difference which demonstrates the limits of the Asilomar paradigm for the management of the implications of this scientific innovation, since it is "too limited in terms of both its participants and its scope" ([20], p. 307). It has even been argued that this paradigm was already inadequate at the Asilomar conference itself, given that at that time the technology of recombinant DNA already raised concerns about its ethical, social, economic and national

security implications. Having failed to include such broader aspects in the risk assessment, concentrating on the technical impacts alone led to the identification of limited solutions which over the years have given rise to strong and widespread controversies and to a hostile attitude of citizens towards biotechnological innovations. A perfect example of this is the negative reaction to genetically modified organisms in the light of, for example, the profound impact that small farmers have experienced in their lives with the marketing of GMOs and the introduction of biotechnological patents. This hostility, therefore, unlike what was initially thought, is not the result of a lack of scientific information on the part of the public but rather of an inadequate management of the complexity of the impact that the use of the recombinant DNA technique would have in the lives of people, and of different views of citizens compared with those of experts on how to live with emerging technologies. Precisely these controversies have led over time to a review of the paradigm of Asilomar, involving additional experts and not just scientists (ethicists, lawyers, sociologists, etc.), and expanding the range of evaluation to include the so-called ethical, legal, and social implications (ELSI). Furthermore, the relationship with the public has also changed, moving from a model of one-way communication, in which the citizen was only a receiver/auditor of expert information (deficit model), to a model of bidirectional communication, in which citizens are active subjects who express their point of view (public engagement).

The Napa conference and the project of the international summit of the American scientific academies are part of this revised Asilomar paradigm. However, even this inclusive paradigm of new aspects has been considered inadequate, given the growing need to democratize policies regarding the relationship between science and society by giving citizens an increasingly active role in all stages of knowledge production, as we highlight in the final part of this work. The reasons for this can be summarized in four points. Firstly, priority is given to safety and effectiveness compared with the other dimensions involved, such as economic issues, ethical and cultural values, social relations—for example, social problems related to the presence of health differences. Secondly, summits continue to be organized where the experts, including experts other than scientists, are in a privileged position compared with that of the public. This procedure does not favor a broad and inclusive public debate regarding the variety of perspectives involved, and nor does it involve and treat the public as an equal subject in the discussion. Thirdly, the intention to involve the public continues to be restricted to the evaluation—in terms of acceptability—of the applications of scientific research and not to the evaluation of research direction. Furthermore, this participation is limited over time, occurring at specific times with no continuity or follow-up. Fourthly and finally, experts continue to proceed with a linear model of risk assessment, assuming that in advance they can define the issues involved and their relative solutions, losing sight of the unpredictability of new issues in social interactions and relationships with technology that may emerge through long-term experiences. Indeed, these experiences may also occur in the very distant future, if one considers that the effects of genetic modifications on the germline can be seen decades after the introduction of this innovation.

In other words, the criticisms raise the crucial question of how to reconcile the traditional model of self-regulation of the scientific community with the ever more urgent need to adopt forms of democratic governance to manage the wide range of ethical, legal and social issues that accompany a technological revolution like that of CRISPR-Cas9 human genome engineering technology. “That leading scientists should call for responsible research is wholly laudable. But the human genome is not the property of any particular culture, nation, or region; still less is it the property of science alone. It belongs equally to every member of our species, and decisions about how far we should go in tinkering with it have to be accountable to humanity as a whole. How might a US or international summit on gene editing attempt to meet that heavy responsibility?” ([21], p. 26)

In December 2015, the International Summit on Human Gene Editing was held in Washington, DC to discuss scientific, ethical, and governance issues associated with human genome editing [25]. At the end of the summit, the organizing committee released a statement regarding the research and clinical use that could proceed within current regulatory and governance protocols. The committee also claimed that it would be irresponsible to proceed with clinical germline genome editing until there has been a demonstration of “safety and efficacy,” a “broad societal consensus about the appropriateness of the proposed application,” and corresponding regulatory oversight. It called upon the “international community” to “strive to establish norms” so as to guide the use of this technology and pointed to the need for an “ongoing international forum”

that "should be inclusive among nations and engage a wide range of perspectives and expertise – including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public" ([26], p. 7).

These conclusions show a certain openness of the scientific community towards the criticisms that some scholars in the months preceding the summit had advanced regarding the reaction of scientists to the emergence of the use of CRISPR-Cas9 on human embryos. Although we continue to proceed referring to the regulatory model of Asilomar, with scientists controlling the definition of both problems and solutions [27], it is clear that there are two new conditions to be met for applications aimed at editing the human genome to be considered acceptable: the acquisition of a broad societal consensus concerning the appropriateness of the proposed application, and the creation of an ongoing international forum, given the global nature of the issues to be addressed. This rethinking does not exclusively concern genome editing issues, where there are strong ethical, anthropological and political controversies, but it is part of a more general reflection on the relationship between science and society that sees the science as closely intertwined with society. Hence, the need to adopt involvement procedures, from the public engagement to participatory science forms such as citizen science, in all fields of emerging technologies. The introduction of these two conditions highlights the awareness of the scientific community that it can no longer evaluate and manage the risks connected to emerging technologies in biomedical research without taking into account the variety of perspectives involved and the need to establish global comparisons and agreements. Therefore, the debate that followed the first international summit on human genome editing focused on considering which governance model can satisfy these two conditions by taking into account some elements of a reticular conception of knowledge. From the considerations that followed, a further enlargement of the perspectives has emerged which include: not only perspectives which, in general, are different from those of the experts, but also perspectives which are in disagreement with the scientific point of view of those who are marginalized, or not directly affected by the scientific innovation at stake; not only global agreements but also agreements that take into account the cultural and moral diversity present in the global community, including minority and non-Western positions.

Regarding the debate concerning the acquisition of a broad societal consensus, the report of the Academies of the American Sciences of 2017, *Human Genome Editing. Science, Ethics and Governance*, devotes an entire chapter to the topic of public engagement, providing guidelines to be followed in order to widen the perspectives to be taken into consideration as much as possible. It is interesting to note that on that occasion it was explicitly recognized that non-experts can make an important contribution to problem management: "members of the audience are able to ask questions and suggest solutions that may not have been imagined by regulators or experts" ([28], p. 127); and the limits of the current modalities in the USA for the involvement of the public are clearly evident. Through these modalities, it is only possible to collect a limited number of perspectives, which are also the views of people already interested in scientific topics—such as patient advocates. These perspectives, therefore, in addition to not being inclusive often do not even fulfil the role of overcoming the bias that can be found in the scientific community. Attention to a more inclusive involvement of the different perspectives involved regarding the engagement methods so far adopted can also be seen in the report of the Nuffield Council of Bioethics *Genome editing and human reproduction: social and ethical issues*, published in 2018, which states that the term inclusive in social debate "means that such a debate needs to attend to the views and values of all of those with an interest, not only those most directly and immediately affected, but also those who may be collaterally affected. In particular, it means attending to the voices of those who do not share the majority interest and who prospective technologies might place in positions of vulnerability, as well as creating opportunity to represent the interests of future generations, whose voices are necessarily absent" ([29], p. 141).

Regarding the proposal to create an ongoing international forum, some scholars have recently launched the idea of creating "a global observatory for gene editing, as a crucial step to determining how the potential of science can be better steered by the values and priorities of society" ([30], p. 436). Behind this initiative, there is the need in the evaluation, which is considered a priority by these scholars, to highlight in the pros and cons of human genome editing a richer range of issues and concerns that tend to be neglected and which instead

have an important impact on people's lives: "[w]e identified the need for a forum to promote sustained international, interdisciplinary and cosmopolitan reflection on several key considerations: what questions should be asked, whose views must be heard, what imbalances of power should be made visible, and what diversity of views exist globally" ([30], p. 436). What is proposed therefore is a reflection that goes beyond the themes established by the scientific agenda and which includes among the perspectives to be taken into consideration even those that do not conform to dominant Western culture, including both scientific and bioethical issues, in order to highlight the variety of cultural and moral perspectives within the global human community. Such an observatory is necessary given the delicacy of the central question regarding the use of the CRISPR-Cas9 system on human germ cells: how to take care of, evaluate and imagine human life, individually, socially and in relation to other forms of life on earth. In this model of governance at global level, scientific consensus does not predetermine the acquisition of social consensus [31].

In the meantime, the scientific community continues to deal with the management of human genome editing governance, continuing to organize international summits. In November 2018, the second international summit was held on *Human Genome Editing* in Hong Kong, organized by the Academy of Sciences of Hong Kong, the U.K. Royal Society, and the U.S. National Academy of Sciences and US National Academy of Medicine. The aim of the summit was "to assess the evolving scientific landscape, possible clinical applications, and attendant societal reactions to human genome editing" [32]. The statement issued by the organizers at the end of the conference refers to a governance model that continues to put the control of the definition of problems and solutions into the hands of the scientists, and the community of experts in general. Specifically, with regard to the editing of human germ cells, the organizing committee concluded "that the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway towards such trials" [32]. At the same time, there has been a new appeal to create an ongoing international forum, whose objectives include favoring a wide public dialogue.

The need not to lose sight of the importance of keeping together and seriously taking these two indications into consideration—on the one hand the rigor with which scientific experiments are carried out and on the other confrontation with the public—seems to be confirmed also in the light of the announcement on the eve of the summit regarding the birth of twins with an embryo modified through the CRISP-Cas9 technique to generate resistance to HIV. This was an unauthorized clinical experiment therefore violating all the criteria of the scientific method. This need was reiterated by a group of researchers, in an article published in the journal *Nature*, with the proposal of "a global moratorium on all clinical uses of human germline editing—that is, changing heritable DNA (in sperm, eggs or embryos) to make genetically modified children" [33].

Conclusions

The comparison between the risk assessment management model in the case of recombinant DNA and in the case of the CRISPR-Cas9 system applied to human embryos is useful not so much, as has been widely argued, to draw attention to the continuity of self-regulation by the scientific community, but rather to reflect on the need to define procedures that meet the criteria of democracy and responsibility towards society. This comparison shows how over the years, there has been a broadening of policy issues that researchers must consider in order to not only be scientifically responsible and produce solid and secure knowledge, but also to conduct socially acceptable research. Although the complexity of the issues involved in the risk assessment of emerging technologies has increased over time, already at the time of the Asilomar conference, all the challenges today regarding the redefinition of the relationship between science and society facing scientists, other experts and society were already present. There are still no definitive conclusions regarding the solutions identified to meet these challenges. It is clear that we need to identify more democratic forms of decision-making so that all of the subjects involved, or at least most of them, whether they be individuals, groups or nations, can voice their opinions. Good practices are such approaches as patient and public involvement (PPI) in health and research, citizen science in environmental and health investigations, and other participatory societal decision-making processes [34–36]. In these approaches, all stakeholders, not just the scientific community, have the opportunity to discuss the potential

risks, benefits and consequences of a research / technology / social and environmental decision or goal before it is developed or implemented. It is a reticular conception of knowledge, in which all the stakeholders have the possibility of mutual interferences during the decision process. However, implementing paths of this nature is not easy. Untimely solutions and a lack of cultural preparation or the simple bureaucratization of decisions are not good translations neither of widespread and correct information nor of a concrete public participation in scientific decisions. The ways to ensure understanding and evaluate public consent must be multiple and realized at different levels (including political, legal and market ones). In the absence of such a path, it is high the possibility that the grand statements and the regulation of risks turn out to be nothing more than an empty echo. In this perspective, Sheila Jasanoff has coined the term bioconstitutionalism [37] to indicate precisely those phases of political history in which the law seeks to give meaning and legal standing in the presence of new materials and new scientific knowledge.

More sources, including the European Union, have called on scientific research to work with a wider range of social groups. Indeed, widespread participation and radical innovation positively influence scientific progress and social development. As outlined in the US National Academy of Sciences 2017 report [28], public participation on this issue should be included in the "general decision-making process" and should include continuous monitoring of public attitudes, lack of information and emerging concerns in "public opinion" [28, p. 137]. In other words, the right of access and better understanding to all phases of the research process and particularly to the evaluation of the results of scientific research and how these results can be used is increasingly becoming a frontier of social equity that can and must be included in a more general expansion of citizenship rights.

The integration between science and democracy, implied in the perspective that we have tried to outline in this paper, is based on the idea that in a technologically advanced society, these two factors are intertwined, giving rise to new rights, new expectations and new values, aimed to guarantee all citizens the right of access to knowledge concerning themselves as members of a democratically directed society. In any case, the lines that will compose and define these new rights are still largely to be traced.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they don't have potential conflicts of interest; the paper is not part of research involving human participants and/or animals; for the characteristics of the paper, no informed consent is required.

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