*Cambridge Quarterly of Healthcare Ethics* (2023), 1–13
doi:10.1017/S0963180123000300

CAMBRIDGE UNIVERSITY PRESS

ARTICLE

# When Is Something an Alternative? A General Account Applied to Animal-Free Alternatives to Animal Research

Koen Kramer[1,2]

[1]Department of Population Health Sciences, Utrecht University, Utrecht, The Netherlands
[2]Section of Communication, Philosophy, Technology and Education, Wageningen University, Wageningen, The Netherlands
Email: k.kramer@uu.nl

**Abstract**

The first "R" from animal research ethics prescribes the replacement of animal experiments with animal-free alternatives. However, the question of when an animal-free method qualifies as an alternative to animal experiments remains unresolved.

Drawing lessons from another debate in which the word "alternative" is central, the ethical debate on alternatives to germline genome editing, this paper develops a general account of when something qualifies as an alternative to something. It proposes three ethically significant conditions that technique, method, or approach X must meet to qualify as an alternative to Y: (1) X must address the same problem as Y, under an appropriate description of that problem; (2) X must have a reasonable chance of success, compared to Y, in solving the problem; and (3) X must not be ethically unacceptable as a solution. If X meets all these conditions, its relative advantages and disadvantages determine whether it is preferable, indifferent, or dispreferable as an alternative to Y.

This account is then applied to the question of whether animal-free research methods qualify as alternatives to animal research. Doing so breaks down the debate around this question into more focused (ethical and other) issues and illustrates the potential of the account.

**Keywords:** 3Rs; alternatives to animal research; germline genome editing; preimplantation genetic diagnosis

## Introduction

The first of the famous "3Rs" from animal research ethics essentially stipulates that experiments on animals, where possible, should be *replaced* by tests on entities that cannot suffer from being experimented on—*reducing* the number of animals used and *refining* experiments becomes relevant only when animal experiments are indicated at all.[1] Although the original formulation of the 3Rs by William M.S. Russell and Rex L. Burch in 1959 avoided using the word "alternative," this first R has come to be interpreted as prescribing the substitution of animal experiments by animal-free alternatives.[2]

Striving to replace animal experiments with animal-free alternatives is arguably a (minimal) ethical requirement that follows from the recognition of test animals' intrinsic value. European Union (EU) law acknowledges this ethical requirement by prescribing the use of nonanimal alternatives wherever possible and urging for the development and validation of such approaches.[3] Member states have accordingly deployed various initiatives to develop state-of-the-art animal-free research approaches,[4] but some still consider current efforts inadequate. Common criticisms are that these efforts have not significantly reduced the number of animal experiments because animal-free alternatives, in practice, are often applied as *an addition to* rather than as a *replacement of* animal experiments,[5] and because such

experiments are inappropriately treated as setting an epistemic "gold standard" that animal-free alternatives must meet.[6,7]

The notion of an "animal-free alternative" thus has ethical, legal, and policy-related significance. When some animal-free alternative to animal experiments has been developed, there is at least an ethical reason to consider replacing the latter, and possibly a legal requirement to actually do so. But a satisfactory account of when an animal-free research method qualifies as an alternative to animal experiments appears to be lacking. While there are many publications that discuss potential alternatives to animal testing,[8,9,10] such publications rarely consider what the word "alternative" means. Moreover, contributions that do raise this question still do not answer the question of when an animal-free method qualifies as an alternative to animal experiments. For example, Joanne Zurlo et al. define a "replacement alternative" as a methodology that "entirely eliminates the need for animal testing" and offer some examples of replacement, but these authors do not explain under which conditions a methodology eliminates the need to experiment on animals.[11] Oliver Flint instead speaks of alternatives as "other tests than the ones we conventionally use, that (…) might be appropriate, possibly more appropriate" than the conventional tests.[12] The obvious question here, which Flint does not address, is when it is appropriate to use animal-free methods rather than animal experiments. Finally, Bernice Bovenkerk and Lonneke Poort ask "What counts as an alternative?" in a section title, but do not actually answer this question; instead, these animal ethicists only offer some examples of moral questions relating to alternatives to animal experiments.[13]

Some might insist that determining whether animal-free methods can be considered alternatives to animal experiments should be done on purely scientific grounds. Defenders of animal research often argue that in vitro methods, for example, do not qualify as alternatives for many types of animal research, because research on cultured cells or organoids does not allow drawing valid conclusions concerning whole organisms.[14,15] They point out that therapies that seem to be safe and effective on the basis of in vitro methods may prove harmful to complete organisms, because these methods cannot adequately model the complex interactions that take place between different systems in actual living beings. For the same reason, in vitro methods could not adequately replace animal experiments that aim to increase scientific understanding of complex biological processes. Similar arguments would apply to other animal-free research methods, such as methods based on computer simulations (in silico research methods).

This paper argues, however, that the question of whether an animal-free method qualifies as an alternative to animal testing cannot be decided solely on the basis of scientific arguments but requires ethical discussion. Drawing lessons from another ethical debate in which the word "alternative" is central, the debate on germline genome editing and its alternatives, this paper proposes three conditions for when something qualifies as an alternative to something else. These three conditions can be summarized in the following principle: *X is an alternative to Y if X offers a reasonably effective and ethically acceptable response to the same problem as Y, under an appropriate description of that problem.* If X meets all these conditions, its relative advantages and disadvantages determine whether it is preferable, indifferent, or dispreferable as an alternative to Y.

Meeting certain epistemic conditions is on this account a necessary but insufficient part of what it means to qualify as an alternative. Ethical conditions also apply: They are relevant independently and co-determine whether epistemic criteria are appropriate. The account developed in this paper not only brings conceptual clarity into discussions on animal-free alternatives by analyzing the notion of "an alternative" but also raises important questions to be addressed in such discussions. How should the problem addressed by animal testing and animal-free alternatives be described? When should a response to this problem be considered "reasonably effective," and when is such a response "ethically acceptable?" How these questions are answered depends in part on the ethical presuppositions made and determines when animal-free methods should be considered alternatives to animal experiments. Importantly, this paper does not answer the question of when animal experiments must from a legal perspective be replaced by animal-free methods. But it does advance the ethical debate on animal-free alternatives and investigate the potential of the account to bring focus into discussions on alternatives more generally.

## Lessons from the Ethical Debate on Human Germline Genome Editing and Its Alternatives

Germline genome editing (GGE) is the application of genome editing techniques such as CRISPR-Cas on early-stage embryos or reproductive cells, with the aim of correcting heritable genetic defects that could lead to disease or disability. In contrast to somatic genome editing, GGE alters the genetic material that an edited human would pass on to future generations. This means that GGE has the potential to prevent the spread of genetic conditions to the next generation as well as later generations. This multigenerational impact is considered not only a potential advantage but also a risk: Any undesirable effects of intended and unintended genetic alterations would also be passed on to and spread among future generations.[16] A central issue in the ethical debate is therefore whether there are alternatives to GGE, with some arguing that clinical applications of GGE should only be developed if reasonable alternatives are lacking.[17,18,19]

The word "alternative" is sometimes used in this context, somewhat loosely, to stand for a technique that can achieve the same ends as a different technique.[20] The technique to which GGE is typically compared is preimplantation genetic diagnosis (PGD), which involves generating embryos by in vitro fertilization and implanting embryos that, according to genetic testing, lack the genetic predisposition(s) of interest. PGD, in many cases, would qualify as an alternative to GGE because both techniques would enable prospective parents to have healthy children that are genetically related to them.[21,22,23]

Although the word "alternative" is typically used to indicate merely that PGD and GGE can often achieve the same ends, Giulia Cavaliere explains more explicitly in what sense these techniques can be considered alternatives: They both "represent a *solution* for those prospective parents whose *problem* is the impossibility of having a *genetically related* and *healthy* child."[24] It is recognized in the literature that how the problem or end is described makes a difference in which options can be considered alternatives. For example, if the end would be described as "not having unhealthy children," then not conceiving could be considered an alternative, and if it would be described as "having healthy children," then adoption could achieve the same end.[25,26] However, these descriptions of the end to be achieved are usually considered inappropriate. Prospective parents generally want to have genetically related yet healthy children, and procreative autonomy is considered ethically important; it is therefore commonly argued that procreative techniques should enable prospective parents to fulfill this wish.[27,28,29,30] But there are also authors who dispute that procreative autonomy justifies developing biotechnologies such as GGE. For example, Dieter Birnbacher questions whether the desire to have genetically related children outweighs the risks and harms involved in applying GGE,[31] and Sarah Franklin argues that this desire rests on outdated notions of kinship.[32] The point is that whether other procreative options count as alternatives to GGE depends on how the end of applying GGE is described, which raises the question of what this end *ought* to be. This is an ethical question.

Even when there is agreement on the proper description of the problem, there can still be disagreement on what counts as a solution to that problem. The main issue here is how effectively, or with what likelihood, a method or technique solves the problem. PGD is sometimes rejected as an alternative to GGE for some conditions because the chance that embryos will be generated that lack the genetic condition is considered too low.[33] This is reasonable: A technique can hardly be considered an alternative solution to a problem if it is unlikely to actually solve that problem. But when is a chance of having healthy children through PGD considered "too low?" Is a 75% probability of success too low? And how about a chance of 25%, or 1%? The answer will presumably depend on a comparison with GGE; it seems reasonable to discard PGD as an alternative only if the chances of success are much higher by using GGE. But the respective chances of success are not all-important. PGD may be justifiably entertained as a possible alternative to GGE on the basis of other considerations. For example, even if GGE may, in certain cases, be more effective than PGD, the associated risk may also be greater.[34,35] Conversely, some have argued that GGE is morally preferable because it involves *treating* rather than *selecting out* (potential) individuals with genetic predispositions for disease.[36] The point is that rejecting either option solely because it has a somewhat lower chance of success would disallow taking any relative advantages of this option into consideration. It thus seems that although a technique's effectiveness in solving a problem (under an appropriate description of that problem) is important, it may qualify as an alternative

solution even if its chances of success are somewhat lower than those of some other technique: A technique may have different advantages that make it worthy of consideration.

This analysis of the ethical debate on GGE and its alternatives offers useful input for a general account of when something is an alternative for something, which could then be applied in a range of contexts, including discussions on animal-free research methods and whether they can be considered alternatives to animal testing. The next section extends upon the analysis offered here to sketch such a general account.

## A General Account of What It Means for Something to Be an Alternative to Something

Abstracting from the preceding analysis of the debate on GGE and its alternatives, a tentative account of when something qualifies as an alternative to something else can be sketched. An alternative is an approach or technique that can achieve the same end or solve the same problem as the technique to which it is compared. However, technique X only qualifies as an alternative to technique Y if it addresses the same problem as Y under an appropriate description of that problem and if it has a reasonable chance of success in solving that problem. This does not mean that X must be at least as likely as Y to solve the problem; other considerations also count in deciding whether a technique deserves to be treated as an alternative.

The preceding analysis thus suggests that X qualifies as an alternative to technique Y only if it meets the following conditions:

(1) X addresses the same problem as Y, under an appropriate description of that problem.
(2) X has a reasonable chance of success, compared to Y, in solving the problem.

However, this provisional account still seems incomplete. Suppose that a young and fertile pair of prospective parents hope to have at least one healthy child but have a 75% chance that any child they conceive will have some serious genetic condition. If the aim of procreative interventions like PGD and GGE is appropriately described as enabling parents to have genetically related and healthy children,[37,38,39] then an alternative approach would be to let these parents conceive in the conventional way and abort every fetus that, according to genetic screening, carries the condition of interest. Even deciding to carry affected fetuses to term and letting them die shortly after birth would seem to qualify as an alternative solution to their problem; given enough time, the couple would, in either scenario, have a good chance of ending up with at least one unaffected child that is genetically related to both parents. Such approaches are rarely even entertained as alternatives to PGD and GGE, however, because they seem so obviously unethical. It seems appropriate to reject such alternative "solutions" outright, which motivates adding a third criterion:

(3) X is not ethically unacceptable as a solution to the problem also addressed by Y.

There can be disagreement, of course, on whether some ethical objection against X is decisive. For example, the fact that PGD involves discarding embryos that are considered unsuitable or superfluous makes PGD unacceptable to some people but not to others.[40,41] The possibility of disagreement on whether this condition is met does not make it any different from the other conditions, however. Whether a description of a problem is appropriate is a normative issue that allows for disagreement, as we have seen earlier, and the same applies to whether a chance of success is reasonable. This does not mean that the conditions proposed are invalid or useless. Rather, these conditions make explicit that the question of whether something qualifies as an alternative to something is an inescapably normative issue and break it down into a number of separate issues.

These three conditions can serve to distinguish between potential responses to a problem that merit further consideration and those that do not. Approaches that address the right problem (appropriately described), that are sufficiently likely to solve it, and that are not obviously unacceptable from an ethical perspective deserve to be compared seriously, while approaches that do not meet all of these conditions

fail to qualify as alternative solutions to the problem and can be rejected outright. This arguably resonates with the pragmatics of presenting something as an alternative to something else. Someone presenting GGE as an alternative to PGD suggests that GGE deserves to be considered seriously as a different (and perhaps better) solution to the same problem.[42] But she may not want to suggest that adoption also deserves discussion as an alternative—she might, for example, discard adoption as an option because it does not enable prospective parents to have children that are genetically related to them. The pragmatic point of presenting alternatives is not to expand the discussion to include all possible approaches to the problem under consideration but only to include those that one considers worthy of serious discussion.

There is more to the pragmatics of proposing something as an alternative to something, however. As explained earlier, PGD has been presented as an alternative to GGE mainly because of the multigenerational risks associated with the latter,[43] while GGE has been presented as an alternative to PGD because the latter could not be applied in some cases[44] and involves discarding viable embryos.[45] In both cases, what is proposed as an alternative is presented as potentially preferable, given certain objections to the other technique. However, it is also possible to present an alternative as equally acceptable, or even just sufficiently acceptable compared to another technique. Some have, for example, argued that prospective parents should, as a matter of reproductive autonomy, have the right to use GGE rather than PGD.[46,47] This argument does not presuppose that GGE is preferable to PGD and only that it would be acceptable for prospective parents to choose the former over the latter.

These different pragmatic aims can be clarified by distinguishing between *indifference* and *preference* relations in subjective comparative evaluations of alternatives.[48] Indifference means that a subject evaluates alternatives as having equal value, while preference means that one alternative is considered better than another. Importantly, indifference does not imply that the alternatives are valued equally in every respect: Alternatives X and Y can also be evaluated as having equal value when X and Y both have some advantage(s) over each but neither advantage is decisive in the subject's comparative evaluation of each alternative.[49] One might, for example, judge that PGD is less risky but also less likely to result in the birth of a healthy child than GGE and end up without a clear preference for either technique. Similarly, when a preference relation does obtain, it does not follow that the preferred alternative is preferred in every respect: The alternative that is valued higher overall may still have some relative disadvantages.[50] Finally, preferring one alternative over the other does not imply that one must consider that other alternative unacceptable. Although one should, according to rational choice theory, choose the preferred alternative, one may consider the other alternative an acceptable choice, for oneself or for others.[51]

An account of what it means for something to be an alternative to something should hence distinguish between different ways of being (considered) an alternative to something: Option X can be an alternative to option Y and be (a) preferred over Y, (b) valued equally to Y, or (c) dispreferred to Y (but still considered acceptable). These different comparative evaluations arguably come into play only when the three conditions that were offered earlier are met. When the first three conditions have resulted in a preselection of options to be considered seriously, the following general criteria determine how these options ought to be ranked:

(4a) If X has some advantages over Y that outweigh any disadvantages that X has relative to Y, then X is a *preferable alternative* to Y.

(4b) If X does not have any advantages over Y that make X overall preferable to Y and X does not have any disadvantages compared to Y that make Y overall preferable to X, then X is an *indifferent alternative* to Y.

(4c) If X has some disadvantages compared to Y that overall outweigh any advantages that X has over Y, but X is still overall acceptable, then X is a *dispreferable alternative* to Y.

It is also possible at this point that X is judged to have disadvantages that make X unacceptable as an approach to the problem to be addressed. In that case, it turns out that, although the approach considered was *prima facie* acceptable and thus apparently met condition 3, it is *ultima facie* unacceptable. The approach then fails to qualify as an alternative to Y on closer inspection.

In sum, *X is an alternative to Y if X offers a reasonably effective and ethically acceptable response to the same problem as Y, under an appropriate description of that problem.* If criteria 1 through 3 are met, the balance of relative advantages and disadvantages determines whether X is preferable, indifferent, or dispreferable to Y. Judgments on the relative advantages and disadvantages of alternatives obviously include ethical considerations—for example, with respect to the acceptability of taking multigeneration risks in GGE or discarding embryos in PGD. But the discussion in this section also shows, perhaps less obviously, that normative considerations are involved in deciding whether some approach to a problem deserves discussion as an alternative in the first place. The account developed is summarized as a flowchart in Figure 1.

## Applying the General Account to Animal Testing and Animal-Free Alternatives

The account developed in the previous section can be applied to the question of when animal-free research methods qualify as alternatives to animal research. Doing so clarifies the concept of "an alternative" that is obviously central in discussions around this question, helps to structure the discussion by breaking the question down into more focused questions, and makes the ethical dimensions of the discussion explicit. At the same time, the application offered in this section substantiates the general account of when some technique, method, or approach qualifies as an alternative to some other technique, method, or approach.

Broadly speaking, the end of animal research is to produce scientific knowledge about biological processes or about the safety and clinical efficacy of (therapeutic) interventions in such processes. On a loose understanding of what it means for something to be an alternative to something, animal-free methods that aim to achieve this same end could be considered alternatives to animal testing. On the

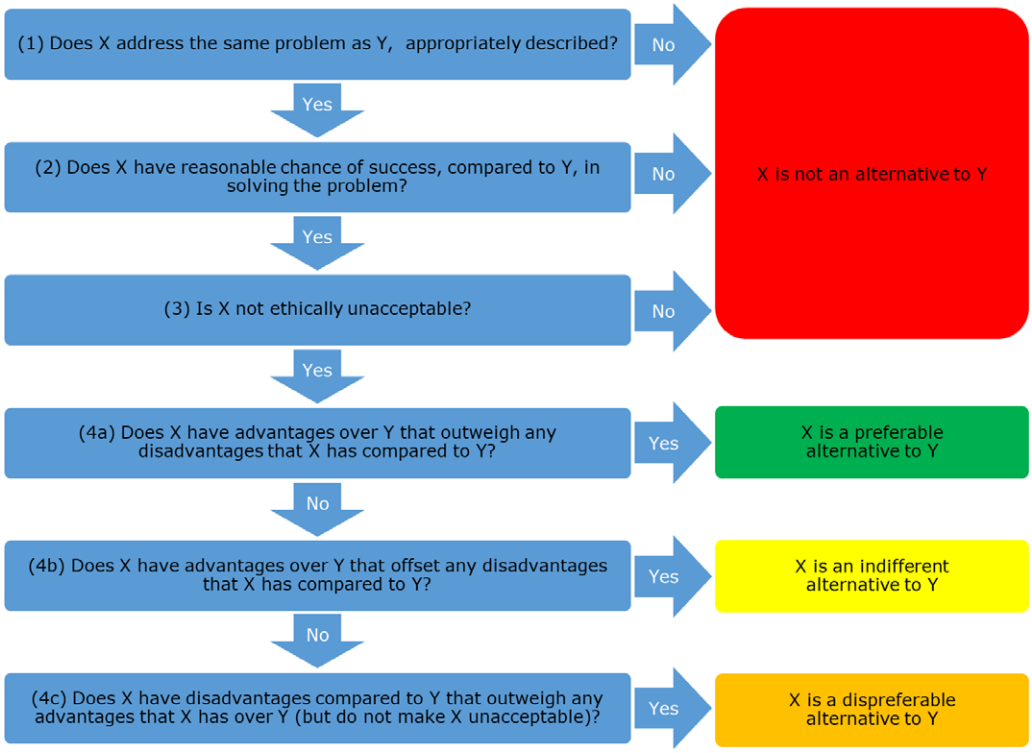


**Figure 1.** Flowchart summarizing the general account of when some technique, method, or approach X qualifies as a preferable, indifferent, or dispreferable alternative to technique, method, or approach Y.

account developed in the previous section, however, more analysis is required to settle whether or not animal-free methods qualify as alternatives to animal experiments.

Following condition 1, one should first consider whether animal-free methods address the same problem as animal experiments, *under an appropriate description of that problem.* Defenders of animal research often argue that animal-free methods do not yield scientific knowledge about the biological processes taking place in complete organisms, nor about the safety and efficacy of interventions in such complex processes.[52,53,54] This suggests that the problem for which animal-free methods ought to be a solution is not appropriately described as "producing scientific knowledge about biological processes or about the safety and clinical efficacy of interventions in such processes": What should apparently be added is that the knowledge to be produced must concern biological processes "as these take place in complete organisms." Adding this clause to the description of the problem would apparently mean that animal-free methods would fail to qualify as a solution.

One might reply, however, that animal-free research methods do (at least indirectly) aim to produce knowledge about biological processes that take place in complete organisms. Granted that cell lines, organoids, computer simulations, and the like are only "models," in the sense that they are simplified representations of the processes going on in actual organisms, their function can be to address questions about such complex processes, for example, questions about the safety and efficacy of pharmaceutical interventions in actual humans with certain pathogenic conditions. It can, of course, be doubted that in vitro or in silico models yield sufficiently reliable or informative answers to such questions. But that does not mean that animal-free research methods do not address the right problem and thus fail to meet the first condition for being an alternative to animal research. Rather, they would address the right problem—appropriately described as "producing scientific knowledge about biological processes or about the safety and clinical efficacy of interventions in biological processes, as these take place in complete organisms"—but possibly fail to be an effective response to this problem.

This leads us straight to the second condition for when something qualifies as an alternative to something, which requires animal-free methods to have a reasonable chance of success in achieving their proper end. As just discussed, it can certainly be questioned whether animal-free methods meet this condition: It can be argued that research on animal-free models does not yield reliable insights with respect to biological processes as they occur in actual organisms, and thus there are no reliable answers with respect to the safety and efficacy of interventions in such processes.[55,56] But it would be too hasty to conclude that animal-free research methods do not meet condition 2 and therefore fail to qualify as alternatives to animal research. Three relevant observations can be made here.

First, the extent to which answers provided by animal-free research methods are reliable may differ depending on the model used and the specifics of the process studied. Even if some models are unsatisfactory in general and some processes are too complex to be studied effectively by animal-free research methods, it does not follow that there are no significant biological processes that can be adequately studied without animal research.[57,58] The question of whether animal-free methods qualify as alternatives to animal research is too broad: The question "Do animal-free methods qualify as alternatives to animal research *for this type of research question*?" is more relevant, in practice.

Second, condition 2 states that animal-free research methods must be *sufficiently* effective approaches to the research problem. Animal-free methods that are reasonably reliable do not necessarily have to be as reliable as animal research to qualify as alternatives.[59] Animal-free methods may deserve serious consideration as alternatives to animal tests on the basis of other relative advantages, notably the avoidance of harm to test animals. When a research method is "sufficiently" or "reasonably" reliable is a normative issue, however, and is arguably sensitive to context. For example, generating a less reliable answer with respect to a therapy's efficacy may be reasonable when mild conditions (such as nail fungus) are involved, but not when addressing serious conditions (such as stroke). The point is that other ethical considerations with respect to a research approach may, in some cases, deserve to be prioritized over epistemic considerations, such as its reliability or scientific validity. This is widely acknowledged in research with *human* test subjects: Ethical requirements set constraints on studies that can override epistemic considerations.[60] At a very minimum, recognizing nonhuman animals as beings who also have intrinsic value requires being prepared to weigh their interests against human interests,[61] and this implies

that the human interest in maximizing the epistemic quality of biomedical research might sometimes have to yield to animal interests.

It deserves note that Article 47 of the European Directive on the protection of animals used for scientific purposes does suggest that animal-free alternatives must be at least as good, from an epistemic perspective, as animal experiments: This Article speaks of animal-free alternatives "as approaches which could provide *the same or higher levels of information* as those obtained in procedures using animals, but which do not involve the use of animals."[62] Settling how Directive 2010/63/EU is to be interpreted is beyond the scope of this paper, but what should be recognized is that the Directive addresses when animal-free alternatives *must by European law* be used *instead* of animal experiments. Even when replacing animal experiments is not obligatory according to current legislation, the question remains whether switching to animal-free research methods is ethically desirable, and this question cannot be answered on the basis of epistemic considerations alone. Neither can ethical questions be avoided by appealing to authoritative formulations of the principle of replacement: any interpretation of the 3Rs that categorically prioritizes the human interest in producing the highest-quality knowledge over animal interests seems objectionably anthropocentric.[63,64]

Third, recall that condition 2 stipulates that approach or technique X must have a reasonable chance of success in solving the problem *compared to* approach Y. If PGD is quite (e.g., 75%) likely to result in healthy and genetically related children for some couple, then GGE must also be relatively likely to have the same outcome to qualify as an alternative to PGD. Conversely, it is unreasonable to expect an alternative to Y to have a high chance of success if Y is not a very effective solution either. It deserves note here that animal research has proven not to be highly reliable, in many areas of biomedical research, when it comes to predicting the safety and therapeutic effectiveness of substances for humans.[65,66,67] Although animal research is still treated as the "gold standard" in biomedical research,[68,69] the inherent biological differences between test animals and humans limit how well findings from animal research translate to humans. A main motivation to develop animal-free methods is indeed to improve success in predicting the outcomes of research on human subjects.[70,71] This suggests that animal-free methods often do not have to be highly reliable to qualify as alternatives to animal experiments.

Turning to condition 3, which stipulates that a method or technique should be (at least prima facie) ethically acceptable to qualify as an alternative, it seems that animal-free research methods easily meet this condition. Animal rights proponents might indeed turn the tables by arguing that most *animal research* fails to meet this condition. Even if certain nonharmful experiments are ethically permissible, most experiments involve harming or killing animals and thereby fail to respect animals' moral rights.[72,73] An animal rights view would thus imply that animal experiments typically fail to qualify as alternatives to animal-free research methods regardless of the reliability or scientific validity of either approach. But even if animal research is not considered categorically wrong, it is difficult to come up with an ethical perspective on which *animal-free* research would be clearly ethically unacceptable, assuming that it addresses the same problem as animal research and does so with a reasonable chance of success.

There are serious objections against one type of research that can in a sense be considered animal-free, namely experiments on *human* test subjects. Using humans in the types of experiments usually performed on nonhuman animals is generally considered unethical,[74,75] except when animal research has already established that the experiments will probably be safe for human subjects. Performing such experiments is also simply illegal in many countries and therefore cannot be an alternative to animal research from a legal perspective either. While the legal limitations on performing experiments on humans are beyond the scope of this paper, there are examples of animal research where conducting a study directly on humans would apparently be acceptable from an ethical perspective.[76]

First, consider studies that mimic interventions in human lifestyles in test animals by subjecting them to different feeding regimens, lighting schedules, and so forth. It is already quite clear that interventions with respect to physical exercise and diet are safe and can be effective against the negative health consequences of overeating, nightwork, and so forth. Studying humans rather than animals may not allow performing a randomized controlled trial with outcome measures that require performing invasive procedures but can be ethically acceptable (and at least in some cases arguably valid enough), given an appropriate study design.

Second, some animal studies aim to "optimize" therapies that are already approved and used in the clinic. It seems ethically acceptable to perform such studies directly in human patients, provided that the therapy's parameters (e.g., dosing, timing, and combination with other therapies) are varied within very safe margins and that general ethical conditions for research with human patients[77,78] are met. The extent to which therapies can be optimized for human patients through animal experiments seems limited anyway, given the biological differences between humans and animals such as mice,[79] which suggests that such therapies often have to be optimized *again* in clinical research.

Establishing exactly when it is acceptable to experiment directly on humans (and when such experiments meet conditions 1 and 2 as well as all legal requirements) is beyond the scope of this paper. The point argued for here is merely that there may well be cases in which experimenting directly on humans rather than doing animal experiments is ethically justifiable. This means that condition 3 does not necessarily exclude that studies with human subjects can qualify as alternatives to experiments performed on animals; whether particular studies with human subjects are ethically acceptable may deserve discussion.

In conclusion, it seems that animal-free research methods can qualify as alternatives to animal research. Even if animal-free research models are simplified representations of complex biological processes, it can be argued that they do (indirectly) address the right problem, which it seems appropriate to describe generally as "producing scientific knowledge about biological processes or about the safety and clinical efficacy of interventions in biological processes, as these take place in complete organisms." This means that condition 1 is met. Whether animal-free research methods meet condition 2 is contentious and is likely to depend on a project's specifics. It is important to note here, though, that the question of whether an approach is *sufficiently* or *reasonably* reliable has ethical as well as epistemic dimensions, and that this criterion does not require animal-free research methods to be at least as reliable as animal research. Moreover, animal research has itself proven not to predict the effects of substances on humans very reliably, at least in some areas of biomedical research; it thus seems inappropriate to treat animal research as a gold standard that would set very high epistemic conditions for when animal-free methods qualify as alternatives. Finally, it seems that animal-free alternatives typically meet condition 3, as there are no clear ethical objections against animal-free research as such. Even experimenting directly on human patients may occasionally meet this condition and qualify as an alternative to animal research.

None of this implies that animal-free research approaches that meet conditions 1–3 are preferable to animal experiments. Conditions 4a–4c clarify that one can also be indifferent between animal-free alternatives and animal experiments or even prefer the latter. To be sure, animal-free alternatives have one clear advantage over animal experiments that deserves recognition from any reasonable ethical outlook: They avoid using animals and causing them suffering?. But at least in a consequentialist framework, this can be offset by the epistemic disadvantages of animal-free research—such as a lower validity or reliability—insofar as these are ethically relevant.[80] Deciding whether animal-free methods are *ultima facie* preferable, indifferent, or dispreferable compared to animal experiments, or indeed whether any such method qualifies as any type of alternative at all, is beyond the scope of this paper; I argued earlier in this section that the answers to such questions are likely to differ according to the research methods considered.

The preceding discussion does challenge treating animal experiments as a gold standard that would set very high epistemic conditions on when animal-free methods qualify as alternatives. Not only is it inappropriate to place high epistemic demands on animal-free alternatives in domains where animal research has proven to be unreliable, but also focusing one-sidedly on epistemic considerations is objectionable. Epistemic desiderata must be weighed against (other) ethical considerations, as is generally recognized in human research ethics, and the recognition of the moral status of animals implies that animal research ethics should be no exception.

This section aimed to bring clarity to debates around animal-free alternatives to animal experiments by applying the account developed in the previous section. Applying conditions 1 through 3 showed that the question of whether an animal-free approach qualifies as an alternative at all—whether preferred, indifferent, or dispreferred—can be broken down into several questions that each has ethically relevant

dimensions. While conditions 4a, b, and c were not applied in an effort to settle whether animal-free research methods that meet conditions 1 through 3 are preferable, indifferent, or dispreferable alternatives to animal experiments, they do show how discussions on animal-free alternatives can be focused further.

## Conclusion

Inspired mainly by discussions about germline genome editing and its potential alternatives, this paper developed a general account of when something (a technique, method, or approach) qualifies as an alternative to something else. It proposed three conditions that can be summed up in the following principle: *X is an alternative to Y if X offers a reasonably effective and ethically acceptable response to the same problem as Y, under an appropriate description of that problem.*

This general account was then applied to the debate about animal-free alternatives to animal research, which, as was noted in the Introduction, suffers from the lack of such an account. In doing so, this paper showed that the question of whether animal-free research methods qualify as alternatives to animal experiments breaks down into several questions that each involve several ethical dimensions. Even the question of whether animal-free research methods are "sufficiently" or "reasonably" reliable or valid is not simply a scientific or epistemic question. The distinction that was made between preference, indifference, and dispreference with regard to alternatives, finally, allows animal-free research methods to still qualify as alternatives to animal experiments even if the latter are preferred for epistemic reasons. An important implication is that ethical discussions with regard to animal-free alternatives cannot be cut short by insisting on the epistemic limitations of animal-free research: Even if animal experiments are preferable from an epistemic perspective, which is not evident for all domains of biomedical research, this does not exclude that animal-free approaches are acceptable or even preferable from a wider perspective.

The account proposed in this paper can thus bring more clarity into debates around animal-free alternatives to animal testing but applies much more widely. In any discussion in which different techniques or approaches to some problem are compared, this paper offers an alternative to using the word "alternative" uncritically.

**Conflict of interest.** The author declares none.

## Notes

1. Curzer HJ, Perry G, Wallace MC, Perry D. The three Rs of animal research: What they mean for the Institutional Animal Care and Use Committee and why. *Science and Engineering Ethics* 2016;**22**:549–65.
2. Tannenbaum J, Bennett BT. Russell and Burch's 3Rs then and now: The need for clarity in definition and purpose. *Journal of the American Association for Laboratory Animal Science* 2014;**54**:120–32.
3. *Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.* Brussels: The Parliament and the Council; 2010; available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0063 (last accessed 30 March 2023). Cf. preamble 12, Article 4 sub-paragraph 1, and Article 47.
4. In the Netherlands, for example, a broad coalition aiming to stimulate a transition to animal-free alternatives has been formed. See Transition Programme for Innovation without the use of animals [Internet]. The Hague: Ministry of Agriculture, Nature and Food Quality; available at https://www.animalfreeinnovationtpi.nl/ (last accessed 9 May 2023).
5. In the EU, the number of animals used in experiments does seem to be declining, but this trend (and how it relates to replacement by animal-free alternatives) is difficult to interpret due to the influence of Brexit and COVID-19. See European Commission [Internet]. *Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in*

*2020*. Brussels: The Commission; 2023; available at https://environment.ec.europa.eu/topics/chemicals/animals-science_en (last accessed 9 May 2023).
6. Netherlands National Committee for the protection of animals used for scientific purposes [Internet]. *Transitie naar proefdiervrij onderzoek: over mogelijkheden voor het uitfaseren van dierproeven en het stimuleren van proefdiervrije innovatie*. The Hague: The Committee; 2016; available at https://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2016/12/15/ncad-advies-transitie-naar-proefdiervrij-onderzoek (last accessed 9 May 2023).
7. Akhtar A. The flaws and human harms of animal experimentation. *Cambridge Quarterly of Healthcare Ethics* 2015;**24**:407–19.
8. Nab J, Balls M, van der Valk JBF, Hendriksen CFM. Reduction and replacement concepts in animal experimentation. In: Van Zutphen LFM, Baumans V, Beynen AC, eds. *Principles of Laboratory Animal Science*. Amsterdam: Elsevier; 2015:335–52.
9. Langley G, Evans T, Holgate ST, Jones A. Replacing animal experiments: choices, chances and challenges. *BioEssays* 2007;**29**:918–26.
10. Homberg JR, Adan RAH, Alenina N, Asiminas A, Bader M, Beckers T, et al. The continued need for animals to advance brain research. *Neuron* 2021;**109**:2374–9.
11. Zurlo J, Rudacille D, Goldberg AM. *Animals and Alternatives in Testing*. New York: Mary Ann Liebert; 1994, at 16.
12. Flint O. What is an alternative? *In Vitro Toxicology* 1997;**10**:165–7, at 165–6.
13. Bovenkerk B, Poort L. Institutionalized ethical assessments of animal experiments. In: Fischer B, ed. *The Routledge Handbook of Animal Ethics*. New York: Routledge; 2019:225–38.
14. Genzel L, Roger A, Berns A, Van den Beucken JJJP, Blokland A, Boddeke EHWGM, et al. How the COVID-19 pandemic highlights the necessity of animal research. *Current Biology* 2020;**30**: R1009–35.
15. See note 10, Homberg et al. 2021.
16. Birnbacher D. Prospects of human germline modification by CRISPR-Cas9 – an ethicist's view. In: Braun M, Schickl H, Dabrock P, eds. *Between Moral Hazard and Legal Uncertainty: Ethical, Legal and Societal Challenges of Human Genome Editing*. Wiesbaden: Springer; 2018:53–66.
17. National Academies of Sciences, Engineering, and Medicine (NASEM). *Human Genome Editing: Science, Ethics, and Governance*. Washington DC: The National Academies Press; 2017.
18. Ranisch R. Germline genome editing versus preimplantation genetic diagnosis: Is there a case in favour of germline interventions? *Bioethics* 2020;**34**:60–9.
19. Ranisch R, Trettenbach K, Arnason G. Initial heritable genome editing: mapping a responsible pathway from basic research to the clinic. *Medicine, Health Care and Philosophy* 2023;**26**:21–35.
20. See note 18, Ranisch 2020.
21. See note 17, NASEM 2017.
22. See note 18, Ranisch 2020.
23. See note 19, Ranisch et al. 2023.
24. Cavaliere G. Genome editing and assisted reproduction: Curing embryos, society or prospective parents? Medicine, *Health Care and Philosophy* 2017;**21**:215–25, at 221.
25. See note 17, NASEM 2017.
26. See note 18, Ranisch 2020.
27. Nuffield Council on Bioethics [Internet]. *Genome editing and human reproduction: social and ethical issues*. London: The Council; 2018; available at https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction (last accessed 30 March 2023).
28. See note 17, NASEM 2017.
29. See note 18, Ranisch 2020.
30. See note 19, Ranisch et al. 2023.
31. See note 16, Birnbacher 2018.
32. Franklin 2013, referenced in NASEM 2017 (see note 12).
33. Gyngell C, Douglas T, Savulescu J. The ethics of germline gene editing. *Journal of Applied Philosophy* 2017;**34**:498–513.

34. See note 16, Birnbacher 2018.
35. See note 24, Cavaliere 2017.
36. See note 24, Cavaliere 2017.
37. See note 24, Cavaliere 2017.
38. See note 17, NASEM 2017.
39. See note 18, Ranisch 2020.
40. Žuradzki T. A situation of ethical limbo and preimplantation genetic diagnosis. *Journal of Medical Ethics* 2014;**40**:780–1.
41. Symons X. Response to Tomasz Zuradzki's 'Preimplantation genetic diagnosis and rational choice underrisk or uncertainty'. *Journal of Medical Ethics* 2014;**40**:779.
42. See note 24, Cavaliere 2017.
43. See note 16, Birnbacher 2018.
44. See note 33, Gyngell et al. 2017.
45. See note 24, Cavaliere 2017.
46. See note 24, Cavaliere 2017.
47. See note 27, Nuffield Council on Bioethics 2018.
48. Hansson SO, Grüne-Yanoff T. *Preferences*. In: Zalta EN, ed. *The Stanford Encyclopedia of Philosophy*. Stanford: Stanford University; 2022; available at https://plato.stanford.edu/archives/spr2022/entries/preferences/ (last accessed 31 March 2023).
49. See note 48, Hansson and Grüne-Yanoff 2022.
50. See note 48, Hansson and Grüne-Yanoff 2022.
51. See note 48, Hansson and Grüne-Yanoff 2022.
52. See note 8, Nab et al. 2001.
53. See note 14, Genzel et al. 2020.
54. See note 10, Homberg et al. 2021.
55. See note 14, Genzel et al. 2020.
56. See note 10, Homberg et al. 2021.
57. See note 8, Nab et al. 2001.
58. See note 9, Langley et al. 2007.
59. Compare Langton R, Holton R. Animals and alternatives. *The Philosophers' Magazine* 2018;**81**:14–5.
60. Cf. World Medical Association (WMA). *Declaration of Helsinki – ethical principles for medical research involving human subjects*. Ferney-Voltaire: The Association; 2022; available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed 30 March 2023).
61. DeGrazia D, Beauchamp TL. Beyond the 3 Rs to a more comprehensive framework of principles for animal research ethics. *Institute for Laboratory Animal Research Journal* 2019;**60**:308–17.
62. See note 3, Directive 2010/63/EU, at Article 47. Emphasis added.
63. See see note 1, Curzer et al. 2016.
64. See see note 61, DeGrazia and Beauchamp 2019.
65. See note 9, Langley et al. 2007.
66. See note 7, Akhtar 2015.
67. Pound P, Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. *Journal of Translational Medicine* 2018;**16**: article 304.
68. See note 7, Akhtar 2015.
69. See note 13, Bovenkerk and Poort 2019.
70. See note 9, Langley et al. 2007.
71. See note 7, Akhtar 2015.
72. Cochrane A. Animal rights and animal experiments: an interest-based approach. *Res Publica* 2007;**13**:293–318.
73. Martin AK. Animal research that respects animal rights: extending requirements for research with humans to animals. *Cambridge Quarterly of Healthcare Ethics* 2022;**31**:59–72.

74. Ferdowsian HR, Gluck JP. The ethical challenges of animal research: Honoring Henry Beecher's approach to moral problems. *Cambridge Quarterly of Healthcare Ethics* 2015;**24**:391–406.
75. Ferdowsian HR, Johnson LSM, Johnson J, Fenton A, Shriver A, Gluck J. A Belmont Report for Animals? *Cambridge Quarterly of Healthcare Ethics* 2020;**29**:19–37.
76. See note 9, Langley et al. 2007.
77. See, for example, Beauchamp TL, Childress JF. *Principles of biomedical ethics*. 8th ed. New York: Oxford University Press; 2019.
78. See note 60, WMA 2022.
79. See note 67, Pound and Hoitinga 2018.
80. See note 61, DeGrazia and Beauchamp 2019.

**Cite this article:** Kramer K (2023). When Is Something an Alternative? A General Account Applied to Animal-Free Alternatives to Animal Research *Cambridge Quarterly of Healthcare Ethics*: 1–13, doi:10.1017/S0963180123000300