“Let us assume that gene editing is safe” – the role of safety arguments in the gene editing debate

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Abstract

This paper provides an analysis of the statement made in many papers and reports on the use of gene editing in humans that we should only use the technology when it is safe. It provides an analysis of what the statement means in the context of non-reproductive and reproductive gene editing and argues that the statement is inconsistent with the philosophical commitments of some of the authors who put it forward in relation to reproductive uses of gene editing, specifically their commitment to Parfitian non-identity considerations and to a legal principle of reproductive liberty.

But, if that is true it raises a question about why the statement is made. What is its discursive and rhetorical function? Five functions are suggested, some of which are more contentious and problematic than others and it is argued that it is possible, perhaps even likely that the 'only when it is safe' rider is part of a deliberate obfuscation aimed at hiding the full implications of the arguments made about the ethics of gene editing and their underlying philosophical justifications.

Keywords

Gene editing, gene modification, gene therapy, harm, non-identity problem, principle of procreative beneficence, reproductive liberty, safety, wrong

“As noted above, we do not believe that sufficient knowledge is available to consider the use of genome editing for clinical reproductive purposes at this time. However, we acknowledge that when all safety, efficacy, and governance needs are met, there may be morally acceptable uses of this technology in human reproduction, though further substantial discussion and debate will be required as detailed below.”¹, p. 42

“Various groups, including ours, agree that numerous technical and safety issues need to be addressed before genome-editing technologies could feasibly be used in reproductive clinical applications.”², p. 159

“The clearest ethical concerns regarding current gene editing techniques is that they are unsafe. The study by Huang and co-authors showed that current gene editing techniques can lead to a large number of off-target mutations. This could cause significant defects and disabilities in any individuals born as the result of the research. While some research suggests there are ways to edit genes that greatly reduce the number of off-target mutations [...], it would be highly unethical to bring modified human embryos to term unless we were very confident that the technique could be used safely. The risk would simply not be justified by any potential benefits.”³, p. 476

“Translating germline modification into clinical trials and society requires time, careful research (involving both the science and ethics) and public deliberation. Broadly, I would propose two conditions for an ethical use of germline engineering. First, there is a requirement for safety. First-in-man use for germline modification is ethically challenging by nature, particularly because the needed evidence to reliably predict risk and benefit (testing in humans) is missing. This needs careful, long-term, interdisciplinary research and sufficient evidence to make the leap from bench to bedside.”⁴, p. 482

Introduction

In ethical debates about the introduction of new technologies into clinical use it is often argued that we should not introduce them as long as they are not safe, but that we should continue basic research and be ready to introduce them when they are safe. In the meantime we should conduct the ethical analysis of their various uses on the assumption that they are safe (or at least safe enough) at the point where they are introduced (let us call this the “only when it is safe’ rider”). This discursive move has also been prominent in the debates about the use of gene editing in humans. It is evidenced by the quotations above; and a recent review of CRISPR Germline Ethics Statements found that of the 61 ethics reports and statement identified almost all mentioned safety concerns and the need for these to be overcome before gene editing can be routinely used in humans⁵.

This paper will analyse 3 issues that are raised by this discursive move. It will ask:

1. What do we mean by ‘safe’, i.e. what harms or wrongs are relevant?
2. Does ‘safe’ have a different meaning in relation to technologies with reproductive implications?

3. In the light of 1 & 2, what are the functions of the 'only when gene editing is safe' discursive move?

In the first part of the paper the analysis of 1 and 2 will initially proceed while bracketing 'reproductive rights' and Parfitian 'non-identity' considerations. The second part of the paper will reconsider 2 in the light of 'reproductive rights' and 'non-identity' arguments. The third part will analyse the implications of considerations of procreative beneficence. And, the fourth and final part will analyse the discursive and rhetorical functions of safety arguments in the bioethical debate about gene modification.

Many official ethics reports concerning gene modification do not contain much ethical argument and it would be problematic to hold them to a high standard of argumentative rigour and philosophical understanding. The focus here will therefore be on the use of the 'only when it is safe' rider in journal articles authored or co-authored by philosophical bioethicists where we can legitimately expect more rigour and knowledge of the philosophical literature, including knowledge of the authors' own previous contributions to that literature.

This is not a paper about the ethics of gene editing. Gene editing technologies enable us to perform a wide range of genetic modifications in humans and animals. Some of these modifications are ethically contentious, but an analysis of which modifications are ethically acceptable and which are not is beyond the scope of this paper.

Safe gene modification

What does it mean to say that a particular gene modification is safe or not safe? What harms, or potentially ethical or legal wrongs are involved?

It is clear that 'safe' and 'unsafe' should be read in a narrow technical sense in this discourse. Safety is conceptualised as being about biological harms that may befall the gene edited organism as a result of the editing and not about wider social or ethico-legal harms. This restricted use of 'safe' is often not made explicit, but it is implicit in distinguishing between safety and governance needs⁶, or in focusing on examples of biological lack of safety⁷. Such a restrictive account of safety may in itself be problematic, but a closer analysis of this issue is outside the scope of this paper where we will accept the narrow biomedical framing of safety.

If we perform gene editing in an organism that organism can be harmed in various ways (let us call these harm₁₋₄):

1. The gene editing may be intended to be harmful
2. The gene editing is technically inefficient and lead to mosaicism
3. The gene editing may be technically efficient (i.e. it makes the desired change in the genome), but may nevertheless turn out to be harmful either on its own, in combination with some other part of the organism's (epi-)genome, or in combination with some infection or environmental exposure, either immediately or during the life time of the organism
4. Off-target genetic changes may be harmful

In relation to clinical use in humans including the research leading up to clinical use we can discount harm₁ and concentrate on harms₂₋₄. No health care professional would perform gene editing with the express intention to harm. If we perform gene modification in humans it will always be in cases where we predict net benefit from the intervention, but where harm may nevertheless occur.

The likelihood and magnitude of these harms can be estimated from research evidence, and may be reducible by future research and development. It is, however as with all technologies unlikely that the risks of these harms occurring can be removed completely. A recent example of a harm falling into category 3 above is the emerging evidence that gene editing is more efficient in cells that are deficient in p53 function, and that this may lead to the selection of gene edited cells with increased risk of tumor formation because p53 is an important tumor suppressor^{8,9}. It was only through research that this problem was identified, and it is only through research that we may find ways to overcome it.

If the gene modification is taking place *in vitro* outside of the body in cultured cells we may have technical procedures for eliminating the risks of harm₂ and harm₄, by modifying cells and then testing and selecting only cells with the correct gene modification, but *in vivo* gene modification is likely always to entail some risk of these harms eventuating.

When is a particular gene modification safe enough to introduce in clinical practice? The simple answer for adults and children in terms of harms, seem to be when we can be reasonably certain that benefits – harms > 0, i.e. when we are reasonably certain of obtaining net benefit from the intervention. There are many in principle and practical questions about how we estimate the benefits and harms quantitatively and about what we mean by ‘reasonably certain’, but resolving them is not relevant to the current analysis of the function of the ‘only when it is safe’ rider.

This threshold must be the right one for approval from a regulator for routine clinical use. A regulator could not allow an intervention to be marketed if there were still significant concerns about its safety. But what if the condition that is targeted by the gene modification is very severe and there are patients willing to take the gamble, before we have sufficient evidence to determine the risk/benefit ratio? Should such patients be allowed to use the gene modification and should researchers be allowed to offer it to patients as experimental treatment? This question is not in principle different from similar questions raised in relation to other therapeutic technologies and methods and discussed in the literature on ‘right to try’ and expedited/expanded access¹⁰⁻¹², and will not be analysed further here. It is, however important to note that it raises important questions not only about the limits, if any of personal autonomy, but also about the balancing between personal liberty to choose and societal interests in having safety and efficacy questions definitively answered through well planned research.

Reproductive safety

Should we understand safety differently if the gene editing is either performed as part of the creation of a child by means of a reproductive technology, or affect the germ cells of the patient?

Bracketing the non-identity problem and considerations of reproductive liberty it seems that there are no relevant differences between the reproductive context and the non-reproductive context in

relation to safety. If gene editing is an intended part of a reproductive project, 'being safe' again simply means that we are reasonably certain that there is net benefit for the child that is the end goal of the reproductive project.

In the directly reproductive context where the entity being edited is either a gamete or an embryo the decision of whether or not to use gene editing will be taken by the people involved in the reproductive project. They choose for someone else, i.e. their future child, and not for themselves and the child cannot consent. But all reproductive decisions by the reproducers are made without the consent of the children, but if they chose a non-safe gene modification intervention (i.e. one where we are not reasonably certain that there is net benefit) they would unjustifiably put the child at risk of harm.

In the indirectly reproductive context where germ cells are edited *in vivo*, either deliberately or as a side effect of some type of *in vivo* somatic gene editing similar considerations about safety and harm apply. We should not introduce genetic modifications into germ cells unless the modifications are unlikely to lead to net harm to any future child created using gametes generated by these sperm cells. Or, if the gene editing is beneficial for the person in whom it is done, but likely to be harmful to future children, then that harm and the reproductive lack of safety should be an important consideration in determining whether to bring the particular type of gene editing into clinical use.

So, the interim conclusion so far is that safety matters both ethically and in relation to regulation, and it matters because we are at risk of causing significant harm if we use unsafe gene editing. The 'only when it is safe' rider therefore seems perfectly justified.

Reproductive safety reconsidered

The reader who is steeped in the Anglo-American bioethical literature will by now probably be screaming 'but why, oh why have you ignored reproductive/procreative liberty and the non-identity problem in the analysis. Because of those two considerations reproduction is different!'

And, it is true that reproduction is different, so different that there is considerably less agreement about our ethical obligations in the procreative sphere than about our general ethical obligations (see for instance the book-length exchange between David Benatar and David Wasserman¹³). So, let us take reproductive liberty and non-identity seriously in our analysis of the meaning of harm in relation to gene editing and imagine a situation where a set of prospective parents want to use gene editing as part of the process leading to the creation of their next child. Do they do something wrong if they use a gene modification intervention that is unsafe in one of the four ways outlined above? We will here bracket the issue that this can only be done as part of technically advanced assisted reproduction and therefore necessarily involve a number of third parties who may or may not have independent ethical importance.

The standard interpretation of the non-identity problem is that if an action (or an inaction) I is necessary for the coming into being of a person P, then P cannot have been wronged by I being performed even if I leads to P being in a harmed state as long as P's state is not so bad that it constitutes 'a life not worth living'¹⁴. P has not been wronged, because you cannot be wronged if, without the action causing the putative wrong being performed, you would not have existed. Some

proponents of non-identity also claim that P cannot be harmed by I, since harm should be understood counter-factually and because I is necessary for P coming into being there is no possible world in which P exists, but in a different un-harmed state. Disentangling the many different possible interpretations of non-identity and its implications and the many and varied highly counter-intuitive consequences that flow from it is far beyond the scope of this paper. What is important in the present context is that if we accept something like non-identity then there is definitely no one who is wronged, and plausibly no one who is harmed by the use of an unsafe gene modification intervention in reproduction, and it is important that this is accepted by some of those who put forward the 'only when it is safe' rider^{15,16} whereas others are more equivocal¹⁷. That there is no wrong done and plausibly no harm created is true of the instant child, and by recursion true of anyone who will ever carry the modification since the first act of modification is a necessary condition for their existence. If the parents are doing something ethically problematic it is only in relation to the state of the world, if the world would, counter factually have been better without the existence of P.

It might be counter argued that not all genetic modifications introduced by gene editing are identity forming or identity changing. Some may, for instance correct a disposition to a condition with very late onset (e.g. Alzheimer's disease) without changing the identity of the embryo that is edited or the person it becomes. And, as a thought experiment we can conceive of gene editing of a part of the genome that has no known functions at all. So, gene editing of an embryo does not necessarily or automatically lead to non-identity. There are many different conceptions of identity at play when considering non-identity. As I have argued in a previous paper in CQ non-identity discussions can involve considerations of numerical, genetic, phenotypical/physiognomical, psychological, and narrative/social identity and it is often important to be clear about what kind of identity we are discussing¹⁸. However, in the present context almost all conceptions of identity lead to the conclusion that the gene editing of embryos affects identity. Not because the actual modification introduced necessarily affects identity, but because it is very unlikely that the same un-edited embryo would ever have been created, implanted, gestated and born.

In a context where gene editing is available to them prospective parents will, with their clinicians plan the IVF + gene editing and it is very unlikely that this will happen at exactly the same time and in exactly the same way as it would have happened if gene editing had not been available, i.e. highly unlikely that exactly the same ova will be retrieved and fertilised by exactly the same spermatozoa. The resulting child will therefore be numerically, genetically, phenotypically, and psychologically different from the child which would have existed (if any) if gene editing had not been available. The only type of identity that might be preserved is an attenuated form of narrative or social identity. The child would still have the same number in the birth order and might still have the same sex, so could still be 'the first son born to Jack and Jill'; but because of the many non-identities it is likely that its narrative would quite quickly and quite substantially diverge from the narrative of the child brought into the world without gene editing being available.

This brings us to reproductive liberty/freedom/autonomy. Reproductive liberty can be understood either as a jurisprudential or an ethical principle or both. The core of reproductive liberty is the claim that our reproductive choices are strongly protected from outside interference, and that this strong protection is justified by the central importance of reproduction to the life plans and personal

identity of people. In his seminal first paper arguing for the importance of procreative liberty John Robertson writes:

“Procreation is a complex activity that develops over time and involves many disparate behaviors. The importance of procreation as a whole derives from the genetic, biological, and social experiences that comprise it. Reproduction is a basic instinct that supplies societies with the members who maintain and perpetuate the social order and who provide services for others. Reproduction also satisfies an individual's natural drive for sex and his or her continuity with nature and future generations. It fulfills cultural norms and individual goals about a good or fulfilled life, and many consider it the most important thing a person does with his or her life.

Claims of procreative freedom logically extend to every aspect of reproduction: conception, gestation and labor, and childrearing.”¹⁹, p. 408

A strong account of reproductive liberty entails that procreative acts are protected from outside interference even in cases where the resulting child is harmed and where the people reproducing are acting in ways that are recognised even by them as ethically wrong and ordinarily blameworthy.

Taken together non-identity and reproductive liberty lead to the conclusion that almost no uses of genetic modification in reproduction can be deemed as unsafe (because of non-identity considerations), and if there are any unsafe uses they can never the less not be prohibited or interfered with in other ways if the procreating parents want to use them (because of reproductive liberty). The only exceptions are gene modifications that are so harmful that they lead to a ‘life not worth living’ since creating such a life is a wrong in all circumstances and also a sufficient justification for overriding even a strong right to reproductive liberty.

Procreative beneficence and the ethics of reproduction

As noted above the ethics of reproduction is immensely complex and the range of positions on the duties of prospective parents contemplating reproduction go from a strong duty not to reproduce (and *a fortiori* not to reproduce in ways involving gene editing) to support for the Biblical injunction to be fruitful and multiply. The part of this wide ranging field that is of relevance here is the question of whether prospective parents have duties to consider the welfare of the child to be in their reproductive decision making. It has been argued that parents have such duties, either a duty not to bring a child into the world that is in a harmed state²⁰, or a stronger duty to follow a principle of procreative beneficence and bring into the world the best child they can²¹. There has been considerable criticism of these posited duties, both in terms of their justification and in terms of their wider implications²²⁻²⁴.

Some of the writers in the gene editing debate are committed to a trinity or triple of positions encompassing non-identity, reproductive (legal) liberty and procreative beneficence. This commitment to the triple is rarely expressed explicitly, but accepting two of the positions simultaneously in argument is quite common. Julian Savulescu and Guy Kahane for instance discuss the interplay between reproductive liberty and procreative beneficence in their seminal paper on the Principle of Procreative Beneficence:

“Talk about moral obligation can be misunderstood in another way. On an understanding of obligation that has its roots in Mill, the existence of an obligation implies the threat of sanction. If this is taken to mean that there is a conceptual tie between obligation and moral disapproval, then PB [Procreative Beneficence] is compatible with such a tie. Egregious procreative choices deserve our disapproval just like other failures to meet one's obligations, such as failure to protect the welfare of one's children. *But although PB claims that parents have a moral reason to aim to have the most advantaged children, when such a choice is possible, this is compatible, at the legal level, with enjoyment of a right to autonomy, including the right to make procreative choices which foreseeably and avoidably result in less than the best child.* Whether the public interest ever justifies legal constraints on reproductive choice is a separate question.” ²⁵, p. 278, reference removed, my emphasis

“We suspect that most people who support Procreative Autonomy do so because they fail to distinguish moral and legal principles. PB is a moral principle. It states what would be morally right or wrong for reproducers to do. *To repeat, PB is not the view that reproducers should be coerced into selecting the most advantaged child, or punished if they don't. Liberal political theory gives strong reasons to grant parents Procreative Autonomy.* But this is compatible with thinking that some legal choices made by parents are nevertheless deeply wrong.” ²⁶, 279, my emphasis

Can the ‘only when it is safe’ rider be justified from the triple of positions? There is a question about whether the triple itself is internally consistent, since there is a possible conflict between non-identity and a duty of procreative beneficence, and a possible conflict between reproductive liberty and reproductive beneficence if reproductive liberty is understood as a moral principle. If the triple of positions is internally inconsistent it follows trivially that the rider is justified, since according to the rules of first order propositional logic any conclusion can be validly inferred from a set of inconsistent premises. But, this is of course not real justification, but pseudo-justification because soundness is undermined by the problem with the premises. In the following we will therefore assume that the triple is internally consistent and take reproductive liberty to be a legal and not a moral principle.

What can be justified is then the claim that prospective reproducers do something which is seriously morally wrong if they use an unsafe mode of gene editing (from procreative beneficence), that this wrong is not directly based on any harm caused to the child (from non-identity), and that although they are doing something morally wrong, they should not be legally prevented from doing it (from a legal understanding of reproductive liberty). This initially looks very much like the ‘only when it is safe’ rider, but this initial appearance is deceptive because the ‘only when it is safe’ injunction is now a purely moral injunction with force only for the prospective reproducers. It is not an injunction aimed at regulators telling them how to regulate, or health care professionals telling them when to refuse to assist in a reproductive project involving unsafe gene editing. Health care professionals can express their disapproval of the reproductive choice (as per Savulescu and Kahane²⁷) or they can remonstrate, reason, persuade or entreat (as per John Stuart Mill just after the famous enunciation of the so-called ‘harm principle’ in *On Liberty*^{28, p.9}), but they cannot refuse to participate unless they give up their neutrality as health care professionals.

The function of safety arguments

The argument seems to have arrived at a point of perplexity. Many of the interlocutors in the debate who seem to be committed to the 'only when it is safe' rider are also committed to the view that only extreme lack of safety can matter when regulating the use of gene editing in a reproductive context. The non-identity problem entails that any future child whose coming into existence has involved gene editing cannot have been wronged by that use of gene editing, and the invocation of reproductive liberty mean that prospective parents have a strong right to reproduce in any way they choose, even if the child that is being brought into existence is in a harmed state. And, even if we commit ourselves to procreative beneficence this has no bearing on when we should allow gene editing to be used in reproductive contexts. So what is the real function of the 'only when it is safe' discursive move?

It could of course be inadvertent ignorance of the underlying inconsistency, i.e. the ethicists in question are not aware or have not yet realised that they are really committed to the view that safety does not matter very much, if at all in reproductive contexts. Or, that if it matters it matters only morally. I think that is unlikely since we are talking about highly intelligent people with excellent philosophical skills, but cannot prove that it is not the case. I will, however proceed on the assumption that they know the content of their own prior writings and their stated philosophical commitments in relation to reproductive ethics sufficiently well to be able to see, almost immediately that there is an inconsistency here. So, something discursively more interesting must be going on. In the following I will analyse five possible explanations for the use of the 'only when it is safe' rider. These five options are not mutually exclusive, two or more may be combined in the explanation of any particular instance of this discursive phenomenon:

1. Simplification of argument
2. Ritualised hand waving
3. 'Consensus building' with non-philosophers (*in casu* scientists)
4. Blurring of the line between philosophical analysis and policy advice
5. Deliberate obfuscation

The simplest and least contentious function of the 'only when it is safe' rider is that it allows the argument about the ethics of eventual uses of gene editing to proceed, while we are bracketing safety issues. So, we can for instance isolate and analyse questions of gene editing for enhancement purposes without having to think about any possible interactions between considerations of purpose and considerations about safety. This is standard philosophical technique, tackling the issues one by one, and is unproblematic, as long as we remember that we have bracketed safety and that all of our conclusions are therefore qualified by safety. That is, if we find that X is ethically unproblematic when safety is bracketed, the conclusion we can draw and state is not that 'X is ethically unproblematic', but that 'X is ethically unproblematic, if gene editing is safe'.

The second function 'ritualised hand waving' conceptualises the 'only when it is safe' rider as an almost automatic invocation, on a par with the Muslim's 'inshallah' finishing of sentences signifying future intentions or 'please' in British English. It has little actual meaning apart from being

something that has to be said every time we discuss a new technology. This can be linked to the observation that it is one of those propositions which it is very difficult to negate and still be taken seriously by polite society. Claiming that we should use gene editing in general, or for a specific purpose 'long before it is safe' simply does not sound like a good idea. We live in a 'risk society' where it is a widely shared value that risks have to be identified and minimised²⁹. On this account any inconsistency with other philosophical commitments is therefore not a real inconsistency because uttering or writing 'only when it is safe' does not, despite surface appearances show any real commitment to the content of the proposition.

The third function of 'consensus building with non-philosophers', *in casu* researchers using gene editing and clinicians wanting to use it, is a plausible explanation for the frequent occurrence of the 'only when it is safe' rider in reports and papers produced by multidisciplinary groups. As explained above negating this rider is pragmatically and discursively difficult, within the general frame of discourses around new technologies. The Precautionary Principle and similar cautionary approaches are part of that general frame, whatever philosophers and regulation theorists might think about them. The philosopher may thus agree to 'only when it is safe' to stay within the standard discursive frame and seem reasonable and sane, with the tactical goal of, for instance getting a more receptive audience in the group for arguments indicating the ethical acceptability of a wide scope of use of gene editing, e.g. not just restricting its use in human to core therapeutic use.

The fourth function of the rider, 'blurring of the line between philosophical analysis and policy advice' has received some attention in the bioethics literature, but usually the problem that is discussed is the reverse of the problem we are analysing here. That is, the discussion is usually about how philosophers overlook or elide the difference between putting forward a radical philosophical conclusion, and advocating for a radical public policy change in the direction of that conclusion^{30,31}. What we have here are philosophers explicitly abjuring themselves of potential public policy implications of their philosophical conclusions. They could say 'safety does not matter very much' for the regulation of reproductive uses of gene editing and advocate that we develop our public regulatory policies accordingly, but instead they say that our policy should be only to use the technology 'when it is safe'. Why this reticence to follow the philosophical conclusions where they lead? Now, it could in an optimistic mode be argued that since gene editing is a relatively new technology what has happened is that philosophical bioethicists have read the papers referenced just above and the many similar papers and books on the gap between philosophical analysis and public policy prescription and have finally realised the significant difference between reaching a philosophical conclusion and advocating for that conclusion as directly implementable public policy. Having had this 'road to Damascus' experience they have therefore started to take account of the specific challenges in public policy development and have stopped immediately transforming philosophical conclusions into policy advice. I leave it to the reader to decide whether this is a plausible account.

We therefore have to consider the fifth and final possible function of the 'only when it is safe' rider, i.e. deliberate obfuscation. By deliberate obfuscation I mean that the rider is inserted primarily in order to hide the full implications of the philosophical positions that underpin the analyses of the ethics of reproductive gene editing, i.e. it is inserted deliberately in order to placate and mislead the reader. Here its function is to signal something like 'don't worry too much about gene editing, or the fairly radical things we say it is OK to do, they are all a long time into the future, and we will only do

them when it is safe to do them'. But this signal elides the difference between biological safety and wider conceptions of safety, and it obscures the wider role of non-identity and reproductive freedom considerations in reaching conclusions on the ethical acceptability of particular reproductive uses of gene editing.

Conclusion

This paper has analysed the statement made in many papers and reports on the use of gene editing in humans that we should only use the technology when it is safe. It has been argued that the statement is inconsistent with the philosophical commitments of some of the authors who put it forward in relation to reproductive uses of gene editing, especially their commitment to Parfitian non-identity and to legal reproductive liberty.

But, if that is true it raises a question about why the statement is made, what is its discursive and rhetorical function? Five functions are suggested, some of which are more contentious and problematic than others and it is argued that it is possible, perhaps even likely that the 'only when it is safe' rider is part of a deliberate obfuscation aimed at hiding the full implications of the arguments made about the ethics of gene editing and their underlying philosophical justifications.

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