Improving the justice-based argument for conducting human gene editing research to cure sickle cell disease

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In a recent article, Marilyn Baffoe-Bonnie offers three arguments for conducting CRISPR/Cas9 biotechnology research to cure sickle-cell disease (SCD) based on addressing historical and current injustices in SCD research and care. I show that her second and third arguments suffer from roughly the same defect, which is that they really argue for something else rather than for conducting CRISPR/Cas9 research in particular. For instance, the second argument argues that conducting this gene therapy research would improve the relationship between SCD sufferers (who are mostly of African descent) and health care providers. But really what is essential in improving this relationship is for those providers to genuinely care and be concerned, and this could be lacking even with the CRISPR research being done. Indeed, this relationship could be improved even without that research being done, as long as there is genuine concern. Thus, this argument actually argues for the need for genuine concern. As for the third argument, one (of two) problems arises because it claims that CRISPR research for SCD should be pursued because the benefits would be shared by even non-research-participants, as non-participants would be encouraged. However, this argues for any research for SCD, not for CRISPR research in particular. I conclude that a better justice-based argument will use only Baffoe-Bonnie's first argument, which is based on historic neglect of an actual cure for SCD (going beyond merely management or transplant therapies).

1 | Introduction

Sickle cell disease (SCD) is caused by a genetic abnormality resulting in defective red blood cells, mostly afflicting patients of African or Mediterranean descent. SCD is held to be a promising candidate for gene therapy research using CRISPR/Cas9, a biotechnology with genome editing capabilities. Marilyn Baffoe-Bonnie recently made the ethical case to pursue this research[1], offering three justice-based arguments that the research would help address historical and current injustices in SCD research and care: 1) by promoting distributive justice in research, 2) by helping to repair the healthcare system's relationship with SCD patients, and 3) by benefiting even those who are not research participants. I will grant that the first argument is sound, but show that the second and third arguments suffer from roughly the same defect. A better justice-based argument for conducting SCD CRISPR/Cas9 research will use only Baffoe-Bonnie's first argument.

A preliminary remark about terminology: I will often use 'gene therapy' rather than 'CRISPR/Cas9 therapy'. CRISPR techniques are currently the most promising among genome editing methods, and so CRISPR often serves as a representative in discussions about gene editing techniques in general. However, I will use 'gene therapy' because the issues in this ethical debate are largely identical whether one is discussing research for CRISPR/Cas9 techniques in particular, or research for *any* future human genome editing techniques to cure SCD.

2 | Baffoe-Bonnie's second argument

Baffoe-Bonnie's second argument is basically this: Because blacks in the US have often not been treated with dignity and respect by healthcare providers, they have historically been distrustful of the healthcare system. Baffoe-Bonnie argues that pursuing SCD gene therapy research would help repair the relationship between healthcare providers and SCD patients, and therefore we should conduct such research. She writes that providers should understand the historical reasons why SCD patients and their families may mistrust them. Further, "[i]f health care providers have historically sensitive conversations with their patients with SCD about CRISPR/Cas9 research, greater trust could be built between them and their patients."[2] Such conversations "would make it more visible to patients with SCD that many different actors understand that more needs to be done to treat and cure their illness."[3] So, conducting research in gene therapy for SCD will give healthcare providers a chance to repair trust and show they understand a cure is needed.

However, this argument is defective because the benefits it points to are not the results of doing research in SCD gene therapy, but the results of sensitive and concerned attitudes on the part of healthcare providers. So, those benefits are not reasons to conduct that research but reasons for providers to be sensitive and to show concern. For instance, suppose that the research is indeed conducted. It is nevertheless possible that healthcare providers inform SCD patients about this emerging research in a demeaning or unconcerned manner. It is even possible that they do not inform SCD patients at all. So, pursuing SCD gene therapy research is compatible with the relationship remaining poor. Hence, conducting that research is not sufficient for repairing the patient-provider relationship.

Nor is it necessary for repairing it. Baffoe-Bonnie points out that the patient-provider relationship has often been poor for two major reasons: First, black patients often feel unwelcome in emergency rooms, and their physical pain is often undertreated. Second, in educating patients and

1 Baffoe-Bonnie, M. S. (2019). A justice-based argument for including sickle cell disease in CRISPR/Cas9 clinical research. *Bioethics* 33 (6):661-668.
2 Ibid., p. 5.
3 Ibid: 5.

their parents about SCD, providers have sometimes communicated in a manner perceived as antagonistic or suspicious.[4] However, these two causes of the poor relationship can be addressed without pursuing gene therapy research; providers can repair the relationship by treating patients with dignity, understanding, and genuine concern as they provide the current conventional therapies for SCD, regardless of whether gene therapy research is done. Further, healthcare providers could communicate to patients a genuine wish that there were a cure for SCD and even relay the need to government agencies, thereby improving the patient-provider relationship. Thus, pursuing SCD gene therapy research is neither necessary nor sufficient for rebuilding patient-provider trust. Indeed, these reflections show that the actual determinant of repairing trust is the providers' attitudes.[5] So, what Baffoe-Bonnie offers is actually an argument for providers to treat SCD patients with dignity and concern, rather than an argument to conduct SCD gene therapy research. Put otherwise, Baffoe-Bonnie of course raises the good point that repairing patient-provider trust is important. Further, the emergence of a promising research program for treating SCD would be as good as any other time to jump-start trust building. However, Baffoe-Bonnie has not shown here that doing gene therapy research for SCD will actually accomplish that goal of repairing trust, but her points instead show that actually providers' attitudes are the key. Thus, here she actually offers an argument for providers to have proper attitudes rather than an argument for doing SCD gene therapy research.

Now if SCD gene therapy research were actually done, one might think it must be effective to some degree in improving the patient-provider relationship. Perhaps knowing about the research may cause the patient to then expect that providers would administer the future cure, and this helps the relationship, regardless of whether providers have a concerned and respectful attitude. However, it is an open question whether this factor would have a non-negligible impact on the relationship. I suspect that after hearing of the research, the patient is far more likely to simply be grateful to the researchers, rather than to think ahead to the providers who would administer any future cure. Regardless, it is an empirical question, and Baffoe-Bonnie has not provided any empirical support that merely knowing about promising new research tends to improve patient-provider relationships. Yet, Baffoe-Bonnie would need to offer such empirical evidence to support this sort of argument in favour of conducting SCD gene therapy research. Thus, in the absence of such empirical support, we are not justified in thinking that merely knowing about SCD gene therapy research being conducted would repair the patient-provider relationship to a non-negligible extent.

3 | Baffoe-Bonnie's third argument

The third argument Baffoe-Bonnie offers is that SCD gene therapy research should be conducted since benefits from that research would impact more than just those subjects participating in the research. This is an argument from "benefit-sharing". Benefit-sharing "is connected to the principle of distributive justice and ensures that there is an ethical and fair distribution of new biotechnologies."[6] She identifies three ways that SCD gene therapy research would promote benefit-sharing.

The first is that the "larger population of SCD sufferers, whether in the States or abroad, should stand to gain" from the research, not just the research participants.[7] However, this is merely an argument to conduct SCD therapy research *of any kind*, not an argument to conduct gene therapy

4 Ibid.
5 Viz. the healthcare sector's responsibility here; patient attitudes are also a factor.
6 Ibid: 5.
7 Ibid: 5.

research in particular, since it is plausible that research for any SCD therapy would potentially benefit all SCD sufferers.[8] Baffoe-Bonnie gives no reason that the benefit of gene therapy research to the larger population of SCD sufferers, relative to its benefit to research participants, is greater than the corresponding relative benefit associated with some other kind of SCD therapy research such as new bone-marrow transplant research.

The second way is that healthcare providers serving SCD patients who are not research participants could nonetheless tell those patients about the gene therapy research. She adds: "In so doing, other patients would have the benefit of feeling included in clinical research and feeling that the gravity of their illness is acknowledged by the clinical and research community."[9] However, the defect identified in the previous paragraph (and indeed Section 2) plagues this argument, since it really argues for something besides gene therapy research *per se*; it argues for researchers and clinicians to genuinely acknowledge the gravity of SCD and convey that to patients appropriately and inclusively. This could be accomplished while discussing even current research of any SCD therapy, not necessarily gene therapy.[10] Thus this argument fails to argue for that research.

The third way Baffoe-Bonnie argues that gene therapy research would bring about benefit-sharing is on grounds of financial accessibility. She reasons that if gene therapy for SCD is inexpensive in the long run, SCD treatment would become more accessible to SCD patients. Instead, "[i]f CRISPR/Cas9 is expensive, adequate benefit-sharing would encourage measures to reduce financial barriers for SCD patients"[11] However, in this case there would be nothing about gene therapy that promotes benefit-sharing, since gene therapy's high cost would instead prevent patients from obtaining the benefit. Thus, her reasoning here is actually an argument, in spite of this, for those more well-off to practice benefit-sharing by subsidizing SCD patients, rather than an argument for doing SCD gene therapy research. But perhaps, as Baffoe-Bonnie had suggested, SCD gene therapy may be inexpensive overall. However, this is merely an assumption. And without justification for it, this third version of the benefit-sharing argument fails. Indeed, there is evidence to doubt the assumption, from an article that Baffoe-Bonnie cites but does not quote: "The ease, cost, and permanency of CRISPR therapies do not necessarily mean they will be cheaper than companion therapies, especially where patents are involved." [12] Thus, neither of the three versions of the benefit-sharing argument succeeds.

8 Baffoe-Bonnie might respond that the benefits she has in mind are not merely better marrow transplants, say, but novel breakthroughs such as a cure for SCD; gene therapy alone provides this. However, recall that the benefit-sharing argument needs to turn upon the *sharing* of research benefits, not the nature of the benefits (unlike her first justice-based argument, which persuasively argues for research likely to yield significant breakthrough benefits for a group underrepresented by research).

9 Ibid: 5.

10 Gene therapy research being done might show that clinicians and researchers truly acknowledge SCD's gravity, since it seeks a cure. But as Section 2 pointed out, the existence of that research is still compatible with them instead being demeaning toward patients. Or, the research might mainly be done from economic or academic motives. Thus, the *sincere acknowledgement* is the primary determinant of the benefit here.

11 Ibid., p.6.

12 Sherkow, J. S. (2017). Focus: Genome Editing: CRISPR, Patents, and the Public Health. *The Yale journal of biology and medicine*, *90*(4), 667-672, p. 668. This quotation appears in the context of comparing costs in the long run.

4 | Conclusion

We saw that Baffoe-Bonnie's second and third arguments for pursuing SCD gene therapy research are defective. However, I grant that her first argument is sound. This is a persuasive distributive justice argument[13] that the historical neglect of SCD research is grounds for research not merely for management/transplant therapies but for a cure, which presently only gene therapy has a chance of providing. She states that the only significant objection is participant-risk in gene therapy research. She responds that if research participants suffer severe SCD and are properly informed about research risks, they should decide if the risks are warranted. She adds, "[i]n doing so, patients with SCD have the dignity to engage in their health-care decisions."[14] So, respecting patient-autonomy makes this risky research permissible, and I think this is an effective response. Therefore, a better justice-based argument for conducting SCD gene therapy research will use only Baffoe-Bonnie's first argument while retaining the patient-autonomy response to defend its permissibility.

13 Baffoe-Bonnie, op. cit. note 1. pp. 4-5.
14 Ibid., p. 7.