Some reprogenetics-related projects you could help with

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Contents

This is a short miscellaneous list of projects that I think would help accelerate germline engineering. This isn't prioritized or comprehensive or anything—it's not the most important projects, but rather just some projects that have occurred to me. Happy to chat with anyone interested.

Project headlines:

- **Deregulation suggestions (law and policy).**
- **Iterated selection scheduling (math/CS problem).**
- **Can genomic vectoring have large effects? (bioinformatics/genetics)**
- **Power of recombinant chromosome selection (math/CS).**
- **Understanding public interest in reprogenetics.**
- **Understanding the regulatory landscape around reprogenetics.**
- **Educating the public about reprogenetics.**

Project details:

- At the moment, the US government is calling for **deregulation suggestions**: https://www.regulations.gov/deregulation. If there's someone who understands how the US Code of Federal Regulations works, and would be up for making a couple submissions, one or two of the policy recommendations here, e.g. CITES treaty and Dickey-Wicker, might be doable: https://berkeleygenomics.org/articles/Policy_recommendations_regarding_reproductive_technology.html
- **Iterated selection scheduling problem.**
  - There's a set of potential methods for strong genomic vectoring that involve combining cells and then having them divide, to alternate between haploid/diploid, or between diploid/tetraploid. That's iterated embryo selection, iterated meiotic selection, and poor man's chromosome selection.
  - There's a difficult math/compsci problem here: how do you actually schedule/select which cell lines to combine, divide, culture, preserve or discard, and sequence/genotype?? It's very complicated. It probably would have to be answered with some big search / machine learning / RL thing. Could be a fun compsci project! I think it should be quite amenable to such methods.
  - I've written a bit about the math here: https://berkeleygenomics.org/articles/Methods_for_strong_human_germline_engineering.html#the-cost-of-poor-mans-chromosome-selection, and I did some preliminary simulations a long while ago, and I'm happy to discuss if you're interested.
- **Can genomic vectoring have large effects?**
  - Many scientists say they are very skeptical that we understand enough about genes for traits to have much effect, even if we could strongly alter the genome. On the other hand, naive extrapolations from current polygenic scores, e.g. for IQ, assuming causality and additivity within the human envelope, say we can have very large effects. Is there a good way to demonstrate or falsify that making many genetic changes should have large effects on polygenic traits? (For comparison, causality can be validated through sibling studies.)
  - Can we look at the tails of phenotypes and/or of polygenic scores, taken from actual living humans, and use clever stats to answer this? More: https://docs.google.com/document/d/1BYiF3_G_oobtjFhuw7QvO0RVTBrgCTCBkrD6nHuAQEc/edit?tab=t.0
  - There are several polygenic scores for traits in animals, e.g. dairy production in cattle. If we had a strong genomic vectoring method, we could test that method to make animals that have been strongly vectored for some trait. We could then observe how much of an effect we had on the

trait—was it roughly linear, as predicted by the polygenic score, or if there's diminishing returns, how quickly are they diminishing? This can't be done right now because we don't have a strong genomic vectoring method that works. Also, it's not completely clear that the results should generalize from, say, dairy production in cattle to intelligence in humans; maybe the genetic architecture of intelligence is somehow different from that of dairy production, in such a way that vectoring has less causal effect.
  - For a given trait, maybe we can argue that genetic variants work through separate pathways. Can we look at known variants associated with some trait, narrow down to just the ones where we understand something about the mechanism (e.g. up or down regulation of expression of some gene, or a tweak to the functioning of some protein), and then check whether the pathways seem likely to overlap / collide or not? This won't be dispositive, but could provide evidence against hypotheses that state that there is some small set of phenotypes that form a "bottleneck" for genetic influences on intelligence.
  - Maybe we can look at historical trajectories in animal breeding. If we have good genotype and phenotype data for agricultural organisms going back one or two decades, maybe we can compare two sets of genes: on the one hand, genes that a polygenic score constructed 10 or 20 years ago would point to as important; and on the other hand, the genes that actually rose greatly in frequency due to several generations of selection for a phenotype. Or we could see if a historical PGS would say that a modern organism ought to have the phenotype that it has, or if the PGS would over- or under-shoot the actual phenotype.

- **Chromosome selection**.
  - Chromosome selection is one possible germline engineering method.
  - I've written about the math of how powerful is CS a little bit here and here. But there's lots more questions to answer, mathy and computer sciency and biological. See the above links and see here for some questions: https://docs.google.com/document/d/1VHrwMYwR6GqQCvJS3m2ObMlZRx1cNmMQcMsed1P1yE/edit?tab=t.0
  - Aside from the math of chromosome selection, there's also the question of how to actually implement it. I and my collaborators have researched this a bunch but we're still not sure; cell biologists or engineers familiar with micromanipulation (or MMCT) could very usefully contribute!

- Legibilizing interest in / demand for / opinion on germline engineering.
  - A core prerequisite for germline engineering is stem cell engineering to make babies (regardless of genomic change). To drive funding to people working on that, possibly it would help to legibilize the strong motivation for that tech, in the world / people, by writing a **nice well-researched comprehensive article, with some quotes from actual people expressing their feelings / telling their stories about fertility problems**. Some preliminary brainstorming and fact-finding here (by me and a collaborator): https://docs.google.com/document/d/1EDVokxJlzoMspgeziKrHVFOiImHBBKyvq1Tz5IPwHfA/edit?tab=t.0
  - Similarly, go through public surveys about germline engineering and summarize the state of public opinion.
  - Similarly, summarize the state of academic / bioethics councils (they may be more in favor, albeit very cautiously and not very outspokenly, than one might expect!).

- Understand the regulatory landscape.
  - Summarize the current laws on the books in various jurisdictions, including states, countries, and international agreements.
  - Summarize current declarations of professional ethics / norms, e.g. among stem cell biologists, geneticists, and reproductive scientists or clinicians.
  - (Note that there are probably existing articles/books reviewing this.)

- There's a ton of stuff that would be helpful to present to the public, e.g. explaining the basics of future germline engineering, or addressing various concerns, or mapping the debates and the talking points. Talented / motivated writers or video makers could help! E.g. making a FAQ or short explainers on YouTube.