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Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer?

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Abstract

Human capital is an important determinant of individual and aggregate economic outcomes, and a major input to scientific progress. It has been suggested that advances in genomics may open up new avenues to enhance human intellectual abilities genetically, complementing environmental interventions such as education and nutrition. One way to do this would be via embryo selection in the context of *in vitro* fertilization (IVF). In this article, we analyze the feasibility, timescale, and possible societal impacts of embryo selection for cognitive enhancement. We find that embryo selection, on its own, may have significant (but likely not drastic) impacts over the next 50 years, though large effects could accumulate over multiple generations. However, there is a complementary technology – stem cell-derived gametes – which has been making rapid progress and which could amplify the impact of embryo selection, enabling very large changes if successfully applied to humans.

Policy Implications

- Recent advances in embryo testing and genomics indicate that embryo selection for modest cognitive enhancement in humans may become feasible within five to ten years. This may spark wider public debate on the desirability of genetic enhancements in humans.
- The effects of conventional embryo selection on the first offspring produced would likely be small relative to past environmental improvements on cognitive ability. However, cumulative effects would be much greater over multiple generations.
- Biomedical research into human stem cell-derived gametes may enable iterated embryo selection (IES) *in vitro*, compressing multiple generations of selection into a few years or less.
- Regulators could speed or slow advance through rules on stem cell research and the private consumer genomics market. Science funding agencies can adjust their support for research into cognitive genomics and stem cell gametes.
- The extent of adoption of human genetic selection may significantly influence national competitiveness and global economic and scientific productivity in the second half of the century.

From carrier-screening to cognitive enhancement

Infantile Tay-Sachs disease is a recessive genetic condition which normally kills before the age of four. When mass genetic testing was introduced into the North American Ashkenazi Jewish community, which suffers from an elevated prevalence of the disease, rates fell by over 90 per cent (Kaback, 2000). Given genetic knowledge, most parents make use of alternative reproductive methods to have healthy children.

Advances in biotechnology are now making it possible to cheaply test for all known single-gene conditions simultaneously. US genomics firm 23andMe offers tests for most common genetic variants, as well as disease alleles, for $99 (23andMe, 2013). As DNA sequencing costs continue to fall, it will become increasingly routine for would-be parents to have thorough information on their own genetic makeup before having children.

The same technologies now used to avert genetic disease also seem likely to enable embryo selection for more complex heritable traits that involve many genes and environmental influences, such as height or cognitive ability. Instead of selecting an embryo based on a single variant, this would involve predicting embryo characteristics using data from many genes, and then selecting embryos using those predictions. The key technical barrier is that existing studies have failed to provide the necessary predictive power, leaving most of the heritability of these traits in study populations unexplained.

Early studies of the genetics of cognitive ability used small samples that could only detect common genetic variants with large effects. However, recent work using genome-wide complex trait analysis suggests that most of the ‘missing heritability’ for cognitive ability can be attributed to a large number of common variants with individually tiny effect sizes (Davies et al., 2011; Benyamin et al., 2013; Plomin et al., 2013). Such variants can be detected with existing methods, but doing so requires extremely large sample sizes to clearly distinguish such weak effects from random noise.

Much larger sample sizes are practical. In the short term, the UK Biobank project has collected survey data and biological samples from some 500,000 individuals, and has hired a firm to perform genetic testing in 2014 (Affymetrix, 2013). The samples are tagged with educational and income data, and a third include a cognitive ability test. The rapidly growing consumer genomics firm 23andMe (2013) already has about 500,000 customers, 90 per cent of whom have opted in to participate in research.[1] In the longer term, as DNA testing becomes a routine part of medical care, data sets of tens of millions of individuals may be assembled from data produced for medical reasons. Such databases could be matched against standardized test scores, educational data, and income to produce extraordinary sample sizes at low marginal cost. Thus, while our understanding of the genetic correlates of cognitive ability is very limited today, it is set to increase dramatically in the coming years.

Impact of cognitive ability

Studies in labor economics typically find that one IQ point corresponds to an increase in wages on the order of 1 per cent, other things equal, though higher estimates are obtained when effects of IQ on educational attainment are included (Zax and Rees, 2002; Neal and Johnson, 1996; Cawley et al., 1997; Behrman et al., 2004; Bowles et al., 2002; Grosse et al., 2002).[2] The individual increase in earnings from a genetic intervention can be assessed in the same fashion as prenatal care and similar environmental interventions. One study of efforts to avert low birth weight estimated the value of a 1 per cent increase in earnings for a newborn in the US to be between $2,783 and $13,744, depending on discount rate and future wage growth (Brooks-Gunn et al., 2009). These individual gains are significant enough that they might make embryo selection for cognitive enhancement a profitable investment, in the vein of prenatal care. They are however small compared to wage increases from environmental influences such as economic development – migrants can increase their productivity and earnings by several hundred per cent by moving from developing to developed countries (Clemens, 2011).

Increases in cognitive ability would have economic impacts other than via personal earnings, e.g. by promoting innovation. For instance, a major longitudinal study of children who scored at the 1-in-10,000 level on childhood ability tests found that 7.5 per cent had achieved tenure at research universities, compared to a tiny fraction of a per cent of the general population, as well as outperforming on a number of other measures, including patents awarded and success in business (Kell et al., 2013). Roe (1953) studied 64 eminent scientists and found median cognitive ability substantially greater than is typical for scientists generally. Cognitive ability is also correlated with nonfinancial life outcomes, including life expectancy, divorce rates, and probability of dropping out of school (Deary, 2012). Some economists have suggested that cognitive ability has large externalities on economic growth at the national level (Jones and Schneider, 2006), though correlations with economic growth also reflect the positive effects of development on cognitive ability through such channels as education, health and diet. An upward shift of an approximately Gaussian distribution of cognitive ability would also have disproportionately large effects at the tails, increasing the number of highly gifted and reducing the number of people with retardation and learning disabilities.

How much cognitive enhancement from embryo selection?

How much cognitive enhancement would be delivered with different numbers of embryos? Within a single generation, there would be rapidly diminishing returns on increasing numbers of embryos, as shown in Table 1.

Standard practice today involves the creation of fewer than ten embryos. Selection among greater numbers than that would require multiple IVF cycles, which is expensive and burdensome. Therefore 1-in-10 selection may represent an upper limit of what would currently be practically feasible. New techniques for maturing eggs *in*

Table 1. How the maximum amount of IQ gain (assuming a Gaussian distribution of predicted IQs among the embryos with a standard deviation of 7.5 points[3]) might depend on the number of embryos used in selection

Selection	IQ points gained
1 in 2	4.2
1 in 10	11.5
1 in 100	18.8
1 in 1000	24.3
5 generations of 1-in-10	< 65 [b/c diminishing returns]
10 generations of 1-in-10	< 130 [b/c diminishing returns]
Cumulative limits (additive variants optimized for cognition)	100 + (< 300 [b/c diminishing returns])

vitro might make the creation of more embryos feasible, though with diminishing returns. If some selection power were expended on traits other than intelligence (e.g. health, longevity, or appearance), the selection left for cognitive traits would be further reduced. Effect sizes would also fall with less accurate measures of the additive genetic effects on cognitive ability.[4]

Offspring created with this technology could make use of it themselves, with effects accumulating across generations.[5] How long could this process continue before severely diminishing returns would set in? Hsu (2012), using data on the number of genetic differences associated with effects on IQ, estimates that the total number of IQ-affecting alleles in an individual could ultimately be shifted by as much as 30 standard deviations. This estimate assumes that the effects are additive and independent even under extreme selection. The 30 standard deviations of genetic difference would correspond to over 20 standard deviations of phenotypic intelligence – a (difficult to interpret) gain of over 300 IQ points. It seems likely, however, that the additivity assumption would break down before this high ceiling was reached, as various pathways of improvement deliver diminishing returns.

While results of that magnitude have been achieved in animal breeding for traits such as milk or meat production (under factory farm conditions), those traits may have been under much less selective pressure than intelligence has been in human evolution. Some intelligence-enhancing alleles may come with unwelcome tradeoffs, explaining why evolution has not already driven them to fixation. Other alterations may offer relatively unmixed blessings, e.g. cutting back the genetic load of harmful new mutations or selecting alleles whose disadvantages no longer matter in industrial societies (Bostrom and Sandberg, 2009). Thus we cannot be confident as to how far the ultimate physiological limits of genetic cognitive enhancement are from the observed capacities of the currently most gifted humans. If the maximum could be increased substantially above the highest levels historically observed in the human population, it is conceivable that new abilities would become possible. Even a small number of such super-enhanced individuals might then be able to have a major impact on the world.

These estimates could change for different populations and environments, as heritabilities vary depending on the population and environment being studied. For example, lower heritabilities have been found among children and those from deprived environments (Beyamin et al., 2013; Turkheimer et al., 2003). Consider that though human height is highly heritable in most within-country studies, yet citizens of rich South Korea stand over 6 cm taller than the North Koreans who once stood taller than Southerners (Pak, 2004). Numerous other environmental effects on cognitive ability have been studied, most notably the large rise in raw IQ scores over much of the world in the past century known as the 'Flynn Effect' (Nisbett et al., 2012).

Stem-cell derived gametes could produce much larger effects

The effectiveness of embryo selection would be vastly increased if multiple generations of selection could be compressed into less than a human maturation period. This could be enabled by advances in an important complementary technology: the derivation of viable sperm and eggs from human embryonic stem cells. Such stem-cell derived gametes would enable iterated embryo selection (henceforth, IES):

1. Genotype and select a number of embryos that are higher in desired genetic characteristics;
2. Extract stem cells from those embryos and convert them to sperm and ova, maturing within 6 months or less (Sparrow, 2013);
3. Cross the new sperm and ova to produce embryos;
4. Repeat until large genetic changes have been accumulated.

Iterated embryo selection has recently drawn attention from bioethics (Sparrow, 2013; see also Miller, 2012; Machine Intelligence Research Institute, 2009) in light of rapid scientific progress. Since the Hinxton Group (2008) predicted that human stem cell-derived gametes would be available within ten years, the techniques have been used to produce fertile offspring in mice, and gamete-like cells in humans. However, substantial scientific challenges remain in translating animal results to humans, and in avoiding epigenetic abnormalities in the stem cell lines. These challenges might delay human application '10 or even 50 years in the future' (Cyranoski, 2013). Limitations on research in human embryos may lead to IES achieving major applications in commercial animal breeding before human reproduction.

If IES becomes feasible, it would radically change the cost and effectiveness of enhancement through selection. After the fixed investment of IES, many embryos could be produced from the final generation, so that they could be provided to parents at low cost.

Rate of adoption and public opinion

The impact of embryo selection technologies will depend on the number of parents who wish to make use of them as well as on political and regulatory choices. Opinion surveys show that embryo selection for intelligence is currently unpopular, except in the context of mental retardation (a demand which could be met with modest selective power, e.g. selecting 1 in 2 embryos).

The history of IVF, however, suggests that applications which were opposed in anticipation can rapidly become accepted when they become live options. Table 2 illustrates some dramatic reversals in American public opinion before and after the 1978 birth of Louise Brown, the first child conceived with IVF.

As the carrier-screening experience shows, a 25 per cent risk of genetic disease for children of informed carriers can motivate parents to use alternative reproductive technologies. It is not immediately obvious what level of cognitive enhancement would offer a comparable benefit. Increased individual earnings alone, a net present value of thousands of dollars per IQ point (see above), could eventually pay back the costs of fairly expensive procedures, but would be most attractive to patient decision-makers able to afford out-of-pocket costs or with subsidized access. Imitation effects or competitive parenting might drive rapid growth in usage: if selected children visibly excel in schooling, the fear that one's children may be left behind in relative terms may be more motivating than absolute advantages. On the other hand, parents using embryo selection would have to trade-off selection for cognitive ability with selection for other traits, such as disease risks, height, athleticism, or personality.

Using IES could deliver much more extreme results, and the fixed costs of using IES to produce enhanced embryos could be spread across large numbers of enhanced children. On the other hand, IES would compromise the typical genetic relationship between parents and children. To avoid negative effects of inbreeding, IES would require either a large starting supply of donors, or the expenditure of substantial selective power to reduce harmful recessive alleles. These factors would tend to push towards IES offspring being less genetically related to their parents (though more related to one another), and could reduce the appeal of IES.

The history of sperm donation suggests this may be a serious barrier. However, there is some demand for the opportunity to raise genetically unrelated children. In 2008, 136,000 children were adopted in the US (Child Welfare Information Gateway, 2011), while 4,247,694 children were born (Martin et al., 2010). Iterated embryo selection embryos might inspire much greater demand because of their exceptional qualities, though adoptive parents motivated by a desire to save children from poor circumstances may be less attracted to IES.

Total impacts on human capital

The impact of genetic selection will clearly depend on how powerful and widely adopted the technology will be. It is helpful to consider a matrix listing some scenarios varying along the two axes (Table 3). (The scenarios assume a developed country context, and robust knowledge of the genetic architecture of cognitive ability. Incomplete knowledge would scale the effects down, as discussed above.)

The table focuses on individual-level effects, but these would be complemented by synergistic effects when many individuals in a society are enhanced. Both positive and negative externalities are likely. For example, if there are a limited set of positions of a certain type (e.g. Nobel laureate) then enhancement of some individuals would create a negative externality in making it harder for non-enhanced individuals to achieve those positions. Positive externalities include innovations used by everyone, increased savings and investment, greater cooperation, and impact on political institutions.[7] On balance, it seems that the positive externalities would dominate – at least this is commonly assumed in the context of other interventions aimed at improving cognitive performance, such as education and removal of neurotoxic pollutants, which are commonly subsidized for this reason.[8]

Table 2. US IVF and embryo selection attitudes

	Approve/Yes	Disapprove/No	Do not know
Personally use IVF for infertility? (Harris, 1969)	18 per cent	76 per cent	6 per cent
Approve IVF for disease/disability? (Harris, 1969)	35 per cent	55 per cent	10 per cent
Personally use IVF for infertility? (1978 Gallup survey post Louise Brown (Mason, 2003))	53 per cent	35 per cent	11 per cent
Approve embryo selection to avert fatal childhood disease? (Kalfoglou et al., 2004)	68 per cent	n/a	n/a
Approve embryo selection for adult-onset cancer? (Kalfoglou et al., 2004)	58 per cent	n/a	n/a
Approve embryo selection for strength or intelligence? (Kalfoglou et al., 2004)	28 per cent	n/a	n/a

Table 3. Some possible impacts from genetic selection with different technologies and rates of adoption for cognitive enhancement[6]

adoption / technology	'IVF+' Selection of 1 of 2 embryos [4 points]	'aggressive IVF' Selection of 1 of 10 embryos [12 points]	'*in vitro* egg' Selection of 1 of 100 embryos [19 points]	'IES' [100 + points]
~ 0.25 per cent adoption 'marginal fertility practice'	Socially negligible over one generation. Effects of social controversy more important than direct impacts.	Socially negligible over one generation. Effects of social controversy more important than direct impacts.	Enhanced contingent forms noticeable minority in highly cognitively selective positions.	Selected dominate ranks of elite scientists, attorneys, physicians, engineers. Intellectual Renaissance?
10 per cent adoption 'elite advantage'	Slight cognitive impact in first generation, combines with selection for noncognitive traits to perceptibly advantage a minority.	Large fraction of Harvard undergraduates enhanced. 2nd generation dominate cognitively demanding professions.	Selected dominate ranks of scientists, attorneys, physicians, engineers in first generation.	'Posthumanity' (Bostrom, 2009)
> 90 per cent adoption 'new normal'	Learning disability much less frequent among children. In second generation, population above high IQ thresholds more than doubled.	Substantial growth in educational attainment, income. Second generation manyfold increase at right tail.	Raw IQs typical for eminent scientists 10 + times as common in first generation. Thousands of times in second generation.	'Posthumanity'

Population averages would only modestly change in one or two generations, unless there is wide adoption of powerful versions of the technologies. Continued conventional (nonIES) selection could eventually produce very large average effects, but would face obsolescence from more powerful technologies (such as IES, or artificial intelligence). In our thinking about long timescales, conventional embryo selection may be most relevant as a soft lower bound for the potential of cognitive enhancement. Embryo selection may have a larger effect on the supply of extremely talented individuals, particularly in generations after the first. This could have major impacts on cognitively demanding fields.

Birth rates and maturation times moderate the impacts in the short and medium term. While highly intelligent children often accelerate their educations, they pursue more education in total, producing a lag of over 20 years between birth and entry into the workforce. And since the number births in any given year is small relative to the size of the labor force, even universal enhancement would require several additional decades for enhanced offspring to come to constitute a majority of the workforce (though they might dominate certain professions, such as the sciences, sooner). This suggests practical effects would be concentrated in the second half of the century, although policies affecting the technology and its use would determine the number of children growing up decades earlier. While these lags are long, they are comparable to timescales for other interventions that receive political attention, such as effort to improve lifetime outcomes through prenatal care, preschool and childhood nutrition.

Conclusions

Our analysis suggests that human embryo selection will not be a major factor in world affairs in the medium term unless either it becomes very widely adopted or IES becomes feasible and is used by a nontrivial minority. In either of those cases, however, it would significantly increase world human capital, and, in the case of IES, possibly create individuals with unprecedented levels of cognitive capacity. What does this mean for policymakers?

Policymakers have a number of levers with which to affect the progress of embryo selection, funding for the enabling science and technologies being perhaps the most obvious. Policymakers could also choose whether or not to make large data sets available to researchers studying cognitive genomics. For example, as military or national health records come to contain DNA, they could be correlated with tax records, test scores, and education levels (though obvious privacy concerns arise with such data bases). Regulatory agencies (such as the Food and Drug Administration in the US) could help or hinder the growth of private genomics companies. Grantmakers could increase or decrease their support for research into human gamete production from stem cells, which could affect the number of embryos available for conventional embryo selection and the feasibility of IES. Adoption rates could also be influenced by subsidizing or restricting the use of embryo selection and genetic testing for prospective parents. Precedents and infrastructure could be promoted (or restricted) today, focusing on genetic diseases rather than complex traits.

More abstractly, research into the consequences or ethics of embryo selection could better prepare policymakers to decide whether it is desirable to accelerate or delay this technology, and to develop appropriate regulatory frameworks. In the context of thinking about long-term futures, the possibility of genetic enhancement through the application of existing technologies should make technological stagnation seem less likely (Bostrom, 2013).

Once genetic enhancement of intelligence becomes widely recognized as an imminent possibility, public discussion and debate will likely intensify. Secular concerns might focus on anticipated impacts on social inequality, the medical safety of the procedure, fears of an enhancement 'rat race', rights and responsibilities of parents *vis-à-vis* their prospective offspring, the shadow of 20th century eugenics, the concept of human dignity, and on the proper limits of state involvement in the reproductive choices of their citizens. (For a discussion of the ethics of cognitive enhancement, see Bostrom and Ord, 2006; Bostrom and Roache, 2011; Sandberg and Savulescu, 2011.) Some religious traditions may offer additional concerns, including ones pertaining to the use of embryos in IES.

The space of possible policies is large: from prohibition to neutrality to strong subsidy and active promotion. Debates about the desirability of germline cognitive enhancement may not have the same outcome in all countries and jurisdictions. Countries that take a negative view may worry about losing international competitiveness. While immigration could be used to import a cognitive elite into countries that ban the use of genetic enhancements domestically, this may not appear a satisfactory means of addressing a relative cognitive impoverishment. There might therefore be demands for a common set of global rules. Whether any strong form of global coordination would be desirable or feasible remains an important question.

Embryo selection for the enhancement of cognitive capacity or other human traits deserves a place in discussions along with other long-term issues such as demographic trends, sustainability, science and technology policy, global climate change, geostrategic shifts, inequality and intergenerational mobility, and long-range financial planning (pension systems, national debts). Enhancement of human capital, in addition to being an important issue in its own right, would interact quite strongly with all of these other long-term issues, since human problem-solving ability is a factor in every challenge we face.

Notes

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1 The continued growth of private consumer genomics firms like 23andMe might be slowed in the US as a result of regulatory actions.

2 The concept of intelligence and the use of IQ as a measure of it have been extensively debated and studied, though significant controversies remain. For reviews of the state of psychological knowledge on IQ, see Neisser et al., 1996 and Nisbett et al., 2012.

3 The standard deviation of IQ in the population is about 15. Davies et al. (2011) estimates that common additive variation can account for half of variance in adult fluid intelligence in its sample. Siblings share half their genetic material on average. Thus, in a crude estimate, variance is cut by 75 per cent and standard deviation by 50 per cent. Adjustments for assortative mating, deviation from the Gaussian distribution, and other factors would adjust this estimate, but not drastically. These figures were generated by simulating 10 million couples producing the listed number of embryos and selecting the one with the highest predicted IQ based on the additive variation.

4 But note that the power of embryo selection increases sublinearly with the number of genetic variants identified, i.e. it is 'front-loaded' since when fewer variants are identified more selection power can be applied to them.

5 Interestingly, part of the increase in the number of people above high ability thresholds will 'lag by one generation'. This is due to a statistical property of truncation selection on a Gaussian distribution. If one selects 1 out of n embryos, the number of individuals meeting some high threshold must increase by less than n-fold in the first generation. In the next generation, the portion meeting high thresholds could increase by orders of magnitude, depending on the threshold.

6 Rounding up, and again assuming a Gaussian distribution of identified additive genetic effects with a standard deviation of 7.5 IQ points.

7 Jones, 2011

8 Compare Bostrom and Ord, 2006.

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