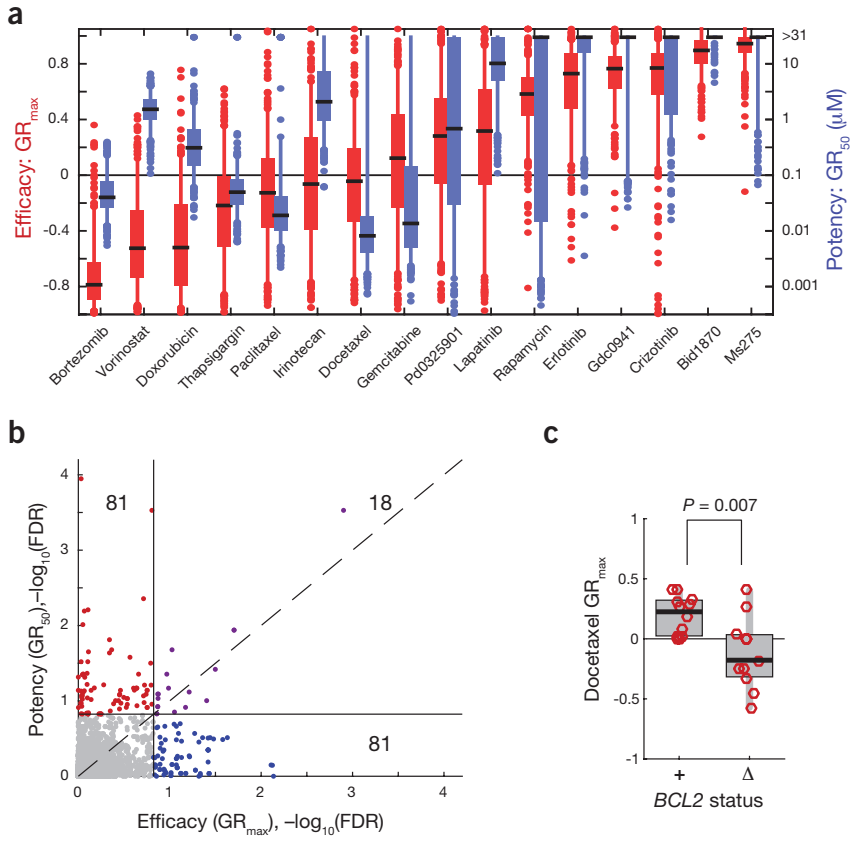

Figure 2 Variation in efficacy and genomic enrichment based on GR_{max} values in the gCSI data set. (**a**) Distribution of GR_{max} and GR_{50} values for each drug across all cell lines. GR_{50} values are capped at 31 μM. (**b**) GR_{50} and GR_{max} enrichment by genomic alteration for each drug and tissue. Numbers represent significant (FDR < 0.15) associations for GR_{max} alone (red dots), GR_{50} alone (blue), or GR_{max} plus GR_{50} (purple). (**c**) Distribution of GR_{max} values for docetaxel in ovarian cancer lines based on *BCL2* deletion status. Rank-sum *P*-value is reported. ($n = 23$).

correlation between gCSI and CTRP data sets is significantly increased using GR_{AOC} rather than AUC as a response metric ($P = 1.3 \times 10^{-3}$, Student's *t*-test; **Supplementary Fig. 4**).

And third, efficacy as measured by GR_{max} and potency as measured by GR_{50} differ at a biological level, carry complementary information (low mutual information), and are associated with largely non-overlapping genetic alterations. In principle, variation in potency and efficacy can be captured by integrating across dose–response curves (GR_{AOC}), but we find that information content is maximized if GR_{50} and GR_{max} are considered independently.

Because the ultimate purpose of antineoplastic drugs is to kill cancer cells[13], and high potency is no guarantee of good efficacy, we propose that the best drugs and most important pharmacogenomic associations are not those associated with low IC_{50} values, but rather those that result in the most negative GR value at clinically relevant drug concentrations (e.g., C_{max}). Relating *in vitro* measures of drug sensitivity to *in vivo* responses remains challenging[17], but for this to have any chance of success it is essential that *in vitro* data are as informative and reproducible as possible.

Editor's note: This article has been peer-reviewed.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

AUTHOR CONTRIBUTIONS
M.H., M.N., and P.K.S. conceived this study and wrote the paper. M.H. performed the analyses. This work was supported by NIH grant U54-HL127365. We thank J.W. Gray, R. Bourgon and colleagues at Genentech, and S. Schreiber for helpful discussions.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

Marc Hafner, Mario Niepel & Peter K Sorger

HMS LINCS Center, Laboratory of Systems Pharmacology, Department of Systems Biology, Harvard Medical School, Boston, Massachusetts, USA.
e-mail: peter_sorger@hms.harvard.edu

1. Hafner, M., Niepel, M., Chung, M. & Sorger, P.K. *Nat. Methods* **13**, 521–527 (2016).
2. Haibe-Kains, B. *et al. Nature* **504**, 389–393 (2013).
3. CCLE Consortium & GDSC Consortium. *Nature* **528**, 84–87 (2015).
4. Harris, L.A. *et al. Nat. Methods* **13**, 497–500 (2016).
5. Niepel, M., Hafner, M., Chung, M. & Sorger, P.K. *Curr. Protoc. Chem. Biol.* **9**, 55–74 (2017).
6. Hafner, M., Niepel, M., Subramanian, K. & Sorger, P.K. *Curr. Protoc. Chem. Biol.* **9**, 96–116 (2017).
7. Haverty, P.M. *et al. Nature* **533**, 333–337 (2016).
8. Im, H.K. *et al. PLoS Genet.* **8**, e1002525 (2012).
9. Choy, E. *et al. PLoS Genet.* **4**, e1000287 (2008).
10. Eichhorn, P.J. *et al. Cancer Res.* **68**, 9221–9230 (2008).
11. Rozenblatt-Rosen, O. *et al. Mol. Cell. Biol.* **25**, 612–620 (2005).
12. Fallahi-Sichani, M., Honarnejad, S., Heiser, L.M., Gray, J.W. & Sorger, P.K. *Nat. Chem. Biol.* **9**, 708–714 (2013).
13. Letai, A. *Clin. Cancer Res.* **21**, 5015–5020 (2015).
14. Fisher, R.I. *et al. N. Engl. J. Med.* **328**, 1002–1006 (1993).
15. Oakes, S.R. *et al. Proc. Natl. Acad. Sci. USA* **109**, 2766–2771 (2012).
16. Seashore-Ludlow, B. *et al. Cancer Discov.* **5**, 1210–1223 (2015).
17. Johnson, J.I. *et al. Br. J. Cancer* **84**, 1424–1431 (2001).

The illusion of control in germline-engineering policy

To the Editor:

The arrival and rapid adoption of the clustered, regularly interspaced, short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9) system[1] has sparked ethical and societal controversy around genome editing of the human germline. Here, I point out the fallacy that such technologies and their applications can be globally prohibited on the basis of universal ethics and bans—the so-called 'illusion of control'. A look at previous technological developments suggests instead that differentiated and multi-faceted approaches that take into account the broadest range of possible ethical and social issues would be preferable for the oversight of CRISPR–Cas9 germline engineering. Such an approach would not only be more effective but also ensure that society has the greatest chance of capitalizing on potential opportunities of the technology.

To date, the CRISPR–Cas9 technique has been used to edit the genomes of (non-viable) one-celled human embryos[2,3]. The first of these genome-editing studies

published in the spring of 2015 prompted debate from within the field and by national academies about not only safety issues (such as off-target effects) but also ethical-moral questions. As a result, calls and statements have been released urging researchers to cease performing CRISPR–Cas9 experiments on human germ cells in a clinical context until safety issues have been resolved and the ethical and social implications of directed germline modifications broadly discussed among diverse societal groups and the public[4–6]. In February 2017 a report by the US National Academies of Sciences, Engineering, and Medicine concluded that clinical trials might be permitted and outlined criteria for a strict regulatory framework. These include the restriction to preventing a serious disease, credible pre-clinical and/or clinical data on risks and potential health benefits, or long-term, multigenerational follow-up (that still respects personal autonomy)[7]. Furthermore, several groups have suggested the need to develop norms and harmonize regulations internationally or globally[5,6].

Among the numerous ethical and social challenges of genome editing and its potential applications, a key unresolved issue relates to the notion that certain technologies or applications can be prohibited globally. The notion of banning technologies or applications worldwide has come to the fore as calls have grown for regulating germline editing in humans. The central assumption underlying this notion is that technologies can be prohibited—continuously or until they are 'safe enough'—and, moreover, that this can be done globally.

Considering reproductive technology as a whole, history provides several examples of procedures that prompted controversy due to ethical (including safety) or moral concerns once they became technically feasible. These include the use of assisted-reproduction techniques (ARTs), such as *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and pre-implantation genetic diagnosis (PGD). As time has passed, these technologies have become more and more widely adopted and accepted across the globe. Today, they have come into use, even in countries where they were initially prohibited for considerable time periods (e.g., Costa Rica, which only effectively lifted its ban on IVF in 2016; and Germany, which only granted conditional permission for PGD in 2011).

In 2015, the United Kingdom approved therapeutic approaches that involve three-parent mitochondrial genome replacement (MGR) in egg cells or one-cell embryos, which thus entail inheritable changes to the human germline. Furthermore, in the Ukraine, MGR has been applied to treat infertility, with a first baby girl reported to have been born early this year[8]. Similarly, US fertility researchers recently announced that they had conducted MGR in Mexico to prevent mitochondrial disease in a boy born last April[9].

An expert panel recently convened by the US Food and Drug Administration (FDA) concluded that clinical investigations of MGR are ethically permissible, though only under strict conditions, for example, if restricted solely to male embryos, which cannot pass on mitochondrial DNA to later generations[10]. Yet, by the time this article went to press, MGR therapy was still effectively banned in the United States owing to an FDA decision in 2001 (http://bit.ly/2q2898X) because of concerns over safety issues such as negative effects from mitochondrial heteroplasmy and mitochondrial–nuclear mismatches. The decision was made in response to ART applied in several fertility clinics that involved the transfer of egg cytoplasm (including mitochondria)[11]. The decision indicates that the use in therapy of human cells "involving the transfer of genetic material by means other than the union of gamete nuclei" requires application to the FDA for permission.

Even the idea that technologies can be banned or prohibited until they are proven by research to be 'safe enough'—at least in the context of reproduction and/or therapies—appears to be disputable. What safe enough means may in practice be as much a question of perception involving different values and interests (and weighing perceived benefits against perceived risks) as it is one of available 'strictly scientific' evidence or numbers (should they be available at all before first clinical applications). An example may be the decisions for the first ART via ICSI by four couples after 3–13 years of unsuccessful trials with traditional ART methods, even though only data from rabbits were available[12].

An ambiguous state of global union

Imposing legal regulations that might prohibit the use of ART technology globally also appears non-feasible, at least when ethical or moral arguments stand in the way of new medical opportunities. Even with respect to human somatic cell nuclear transfer—and despite a seemingly broad international scientific consensus against reproductive cloning due to its low efficiency and the unacceptable potential health issues associated with cloned offspring—no binding global convention has been agreed upon. What's more, the resulting non-binding United Nations (UN; New York) "Declaration on Human Cloning" remains ambiguous by calling to "prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life"[13].

The ambiguity in the UN declaration arises from its failure to define or interpret the forms of cloning that are incompatible with human dignity or what human life and human dignity should mean. The reason this ambiguity exists was because UN negotiations had to address the issue that dignity and life have different meanings in different cultures and religions globally[14]. In line with this, regulations vary in different countries or regions of the world, ranging from prohibition of all forms of cloning, to selectively permitting therapeutic cloning, to no official regulations at all (**Table 1**). Furthermore, the Council of Europe's (Strasbourg, France) legally binding "Convention on Human Rights and Biomedicine," which prohibits in its protocol on cloning the creation of "a human being genetically identical to another human being, whether living or dead," has not been signed or ratified by various member states, although it explicitly leaves the interpretation of "human being" to national policies to allow therapeutic cloning where it is accepted[15]. That (reproductive) cloning appears not to have been performed anywhere so far, including in countries where there is no legal ban, may encourage supporters of such international declarations or conventions. However, it can hardly provide evidence that they were instrumental in—or even contributed to—this outcome, especially given the huge technical hurdles that reproductive cloning faces[16].

Illusion of (universal) control

The idea that biological technologies, like CRISPR–Cas9, or their applications can be (continuously) prohibited, and that this can be done globally thus appears to be reminiscent of the 'illusion of control' in psychology—a phenomenon in which people's beliefs in the control are greater than can be actually justified. For instance, people act as if they have control in situations that are actually determined by chance[17]. Similarly, when people envision that they will obtain a certain result that they then achieve,

Table 1 Different supranational and national policies on cloning and germline modification

		Cloning		Germline modification		
		Therapeutic	Reproductive	Research	Clinical	Type of policy
Global, supranational	United Nations Declaration on Human Cloning	Ambiguous (calls for ban if incompatible with human dignity and the protection of human life)		Ambiguous (calls for ban on the application of genetic engineering techniques that may be contrary to human dignity)		Non-binding declaration
	European Convention on Human Rights & Biomedicine	Ambiguous[a]	Banned	Ambiguous[a]	Banned	Legally binding convention
National	Brazil	Banned	Banned	Banned	Banned	Law
	China	Permitted	Banned	Permitted	Banned	Guideline
	Germany	Banned	Banned	Banned	Banned	Law
	India	Permitted	Banned	Banned	Banned	Guideline
	Japan	Permitted	Banned	Ambiguous	Banned	Guideline
	Mexico	Permitted	Banned	Ambiguous	Ambiguous	Law
	Russia	Banned	Banned	No policy	No policy	Law
	South Africa	Permitted	Banned	Ambiguous	Ambiguous	Law
	South Korea	Permitted	Banned	Ambiguous	Banned	Guideline and law
	Ukraine	No Policy	Banned	?	?	Law
	UK	Permitted	Banned	Permitted	Banned (but MGR permitted)	Law
	USA	No specific federal legislation (but individual states prohibit or permit different forms of cloning)		No outright ban by federal law[b] Permitted[c] in some states	No outright ban by federal law[b] Precluded[d]	State laws; federal laws/regulations that address funding and FDA approval

[a]The Convention's protocol on cloning prohibits anyone "to create a human being genetically identical to another human being, whether living or dead." But it explicitly "leaves the domestic laws of the States to define the scope of the term 'human being'" (http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/168). Furthermore, it demands that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants" (Article 13); and that "where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo" (Article 18). [b]However, the FDA has regulatory authority over cloning technology and over cell and gene therapy. Furthermore, research using stem cells derived from human cloning and gene-editing technologies in human embryos are not eligible for government funding. [c]Various states have passed laws that prohibit or permit different forms of cloning or embryo research, whereas some states have no policy or legislation on embryo research and human cloning[30] (http://www.ruf.rice.edu/~neal/stemcell/Sup_Info.html). [d]Though there is no federal law that bans outright genetic modification of the germline, a provision of the Consolidated Appropriation Act (omnibus spending bill) of 2016 prevents FDA from using federal funds to evaluate and/or permit trials related to human embryos "intentionally created or modified to include a heritable genetic modification"[23].

Ambiguous: indicates that it remains unclear from policy documents whether a practice is banned or may be permitted (e.g., if definitions of key terms are left open); banned: signifies that a practice is prohibited (explicitly or implicitly) by national law or guidelines; permitted: indicates that a practice is either allowed (but not regulated) by laws or guidelines or that it is allowed and regulated (e.g., requiring case-by-case licensing by authorities); no policy: denotes that a practice is not considered in policy documents; ?: unknown or unclear whether this practice is addressed by national policies.

Sources: National policy examples are based on original policy documents; the BioPolicyWiki of the Center for Genetics and Society (http://www.biopolicywiki.org/); Supplementary Information to 'World human cloning policies' by Wheat and Matthews (http://www.ruf.rice.edu/~neal/stemcell/Sup_Info.html); the Appendix on State Laws on Human Cloning; ref. 30 and work from Araki and Ishii[19], Isasi *et al.*[20], and Ishii[31].

they frequently overestimate their influence in bringing about the result[18].

It is very unlikely that a global ban across jurisdictions is feasible. Indeed, current regulations related to germline interventions vary considerably across the globe[19,20]. They encompass bans—based on law or less-enforceable governmental or research council guidelines—that prohibit both research and clinical or reproductive applications; or that prohibit clinical or reproductive application only; or that remain sufficiently unclear to raise doubts as to whether they cover human germline gene modification at all (**Table 1**).

In the United States, no federal law describes an outright ban on human germline interventions and work on human embryos, and in some states researchers could do research on embryos with private funding (as was the case with MGR experiments in Oregon in 2012; ref. 21). Yet, there are regulatory means in place that in fact prevent human germline modifications in publicly funded research and in clinical settings. Thus, the US National Institutes of Health does not fund "any use of gene-editing technologies in human embryos" and its Recombinant DNA Advisory Committee (RAC) will not entertain or review proposals for human germline alterations[22]. Furthermore, the FDA has regulatory authority over cell and gene therapy applying to any (not only publicly funded) research and clinical trials in the United States, and the agency has never approved a proposal to modify the germline.

In addition, a renewable provision (that has been extended twice into 2017) of the US Congress's Fiscal Year 2016 omnibus spending bill prevents the FDA from using the budget to evaluate or permit trials with human embryos "intentionally created or modified to include a heritable genetic modification"[23] (see also ref. 24). The bill may thus also affect the FDA's capability to review MGR therapy approaches (see above).

When it comes to developing regulations on whether or under which conditions germline modifications should be permitted, entrenched moral stances and views on ethics will always be confronted by, and weighed against, the hopes and needs of affected people and their families and caregivers. These may include a desire for people to have their 'own' (genetically related) children not suffering the same disease (e.g., deafness or cystic fibrosis) as both parents do, or new fertility treatments that may be (felt to be) needed due to economic or cultural factors. Naturally, the result of the confrontation between societal ethics and individual hopes—be it a strict ban on all forms of human germline interventions or more differentiated

regulations—will strongly depend on the prevalent ethical and moral stances of the societies in which those individuals are found. And these societal ethical or moral stances will differ across the globe. As in the case of cloning, moral stances with respect to the compatibility with human dignity may also be a key issue with respect to germline modification.

The UN Declaration on Human Cloning includes statements on human genetic engineering. But as for its language about reproductive cloning, it remains vague and ambiguous with respect to genetic modification and human dignity, calling for the adoption of "measures necessary to prohibit the application of genetic engineering techniques that may be contrary to human dignity"[13]. Notions of global bans, and maybe even of globally harmonized regulations, on germline interventions—at least of ones that would not be too vague or ambiguous—may thus in fact include features related to the 'illusion-of-control'.

Alternatives to illusions

Features like exaggerated belief in control or in the causal role of one's own intentions, or unrealistic optimism are elements of normal human thought. They can promote motivation, persistence or the ability to care for others[25]. However, when it comes to the development or choice of policies, it may be worth considering that these phenomena could also have a downside: they may entail less 'realistic' and thus less-efficient policies. Thus, policies may be followed that strive to universally, and maybe continuously, ban or prohibit technologies or their application—irrespective of their purpose—on a national level or even globally. But on the basis of the evidence, there is in fact little or no empirical support that such strategies work.

In addition, they may obscure and distract from alternative policy approaches, focusing on processes that we could better or more realistically control. Such processes could be case-by-case evaluations, dealing with specific applications in which we use knowledge and the technologies in question, such as CRISPR–Cas9 genome editing. Developing and delineating tests and standards (including clinical ones) for techniques or therapeutic tools used in the specific context of these applications may be important elements of such evaluations. Furthermore, focusing on concrete applications and conditions should facilitate interpretations and definitions (including legal ones) related to applications and ethical boundaries[20]. In contrast to global regulations or bans based on efforts to 'globalize' ethics that universally disapprove germline applications of genome editing, alternative, more realistic policies would support more case-oriented approaches.

Such policies may in fact benefit from experiences coming from diverse governance schemes or authorities. These may involve state, regional and national regulations, multiple monitoring bodies (both public and private), but also formal and informal bilateral or multilateral interactions and the engagement of stakeholders on various levels. Stakeholders should include not only researchers and ethicists, but also companies and investors, non-governmental organizations, groups of concerned citizens or families who would be involved in deciding, for instance, on (experimental) approaches.

The difficulty of deciding who should be included in such consultations should not be underestimated. For example, it may be important to engage in the policy development processes of not only do-it-yourself biology and biohacker communities as well as biohacker spaces, but also funding sources, such as crowd-funding platforms or investor-supported 'hackubators', even though human germline applications of CRISPR–Cas may not (yet) appear as a goal for these groups[26]. Involving them and their efforts on codes of ethics may be beneficial, not least of all because any bans or guidelines on institutional research or research funding may hardly provide guidance and oversight on such non-institutional activities[27].

These more 'polycentric' patterns of approaches and stakeholders may promote key elements linked to polycentric governance in other contexts, like diverse experimental efforts, enhanced collaboration or mutual monitoring and trust[28]. These elements could be important to facilitate bilateral and multilateral exchange between nations, and gain scientific data and knowledge on safety issues by carefully crafted and monitored laboratory and clinical experimental approaches. But they may also prove beneficial to the development of democratically meaningful deliberation processes. These would need to go beyond the type of expert-dominated summits or one-time public consultations with largely expert-driven agendas (that resulted from calls, including for global action, and statements by various groups[4–6] so far). Furthermore, these processes would need to contribute to understanding risks by continuously revisiting earlier choices and questions, and thus improve policies over time—based on experiences (about hardly predictable interactions between society and technology) from different conditions and involving a wide variety of perspectives[29]. Such deliberation processes may reduce the danger of missing potentially important ethical, social or political implications, and further strengthen mutual trust.

'Illusion-of-control'-like notions of universal ethics and bans on germline applications may thus favor one-dimensional thinking and illusionary policies, harboring the danger of leaving aside potentially more realistic and efficient policy alternatives. The latter type of 'polycentric' approach should be better capable of exploring the opportunities of genome-editing techniques, foster collaboration between countries and enhance the chances to grasp the broad range of possible ethical and social issues that would have to be taken into account by efficient and trust-building policies. They may also require governments, non-profits, investors and corporate managers to invest more effort to understand and experiment with conditions that both foster and ethically guide innovation.

Ensuring that these differentiated and polycentric policymaking strategies take into account the realities of 'manyness' (i.e., societal differences in values and interests across the globe) would mean tailoring regulations around specific conditions rather than rejecting applications of technologies as a whole. Such an approach to regulations would not only allow space for experimental efforts that generate important scientific data (e.g., on safety issues), but also reduce incentives for researchers to move to countries with more lax standards or less stringent oversight. At the same time as they allow research to progress, they would also allow meaningful democratic deliberation processes on futures with genome-editing applications that people may, or may not, want.

Harald König

Karlsruhe Institute of Technology, Institute for Technology Assessment and Systems Analysis (ITAS), Karlsruhe, Germany.
e-mail: h.koenig@kit.edu

ACKNOWLEDGMENTS

I am indebted to D. Frank for discussions and critical reading of the manuscript.

1. Ledford, H. *Nature* **522**, 20–24 (2015).
2. Liang, P. *et al. Protein Cell* **6**, 363–372 (2015).
3. Kang, X. *et al. J. Assist. Reprod. Genet.* **33**, 581–588 (2016).
4. Lanphier, E., Urnov, F., Haecker, S.E., Werner, M. & Smolenski, J. *Nature* **519**, 410–411 (2015).

5. Baltimore, D. *et al. Science* **348**, 36–38 (2015).
6. Olson, S., ed. *International Summit on Human Gene Editing: A Global Discussion* (National Academies Press; 2016).
7. Committee on Human Gene Editing. Human Gene Editing (National Academies Press; 2017).
8. Coughlan, A. *New Scientist* https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/ (2017).
9. Reardon, S. *Nature* http://www.nature.com/news/three-parent-baby-claim-raises-hopes-and-ethical-concerns-1.20698 (2016).
10. National Academies of Sciences, Engineering, and Medicine. www.nationalacademies.org/hmd/Reports/2016/Mitochondrial-Replacement-Techniques.aspx (National Academies Press, Washington, DC, 2016).
11. Barritt, J.A., Brenner, C.A., Malter, H.E. & Cohen, J. *Hum. Reprod.* **16**, 513–516 (2001).
12. Palermo, G., Joris, H., Devroey, P. & Van Steirteghem, A.C. *Lancet* **340**, 17–18 (1992).
13. UN General Assembly. http://www.un.org/Docs/asp/ws.asp?m=A/RES/59/280 (2005).
14. Arsanjani, M.H. *Am. J. Int. Law* **100**, 164–179 (2006).
15. Council of Europe. http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/168 (1998).
16. Chung, Y.G. *et al. Cell Stem Cell* **14**, 777–780 (2014).
17. Langer, E.J. *J. Pers. Soc. Psychol.* **32**, 311–328 (1975).
18. Miller, D.T. & Ross, M. *Psychol. Bull.* **82**, 213–225 (1975).
19. Araki, M. & Ishii, T. *Reprod. Biol. Endocrinol.* **12**, 108 (2014).
20. Isasi, R., Kleiderman, E. & Knoppers, B.M. *Science* **351**, 337–339 (2016).
21. Tachibana, M. *et al. Nature* **493**, 627–631 (2013).
22. Collins, F. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos (NIH, 2015).
23. US Congress. https://www. congress.gov/bill/114th-congress/house-bill/2029/text (2015).
24. Cohen, I.G. & Adashi, E.Y. *Science* **353**, 545–546 (2016).
25. Taylor, S.E. & Brown, J.D. *Psychol. Bull.* **103**, 193–210 (1988).
26. Brown, K.V. *Fusion TV* http://fusion.net/story/285454/diy-crispr-biohackers-garage-labs/ (2016).
27. Kuiken, T. *Nature* **531**, 167–168 (2016).
28. Ostrom, E. *Glob. Environ. Change* **20**, 550–557 (2010).
29. Jasanoff, S., Hurlbut, J.B. & Saha, K. *Issues Sci. Technol.* **32**, 25–32 (2015).
30. Anonymous. *The New Atlantis.* http://www.thenewatlantis.com/publications/appendix-state-laws-on-human-cloning (2015).
31. Ishii, T. *Trends Mol. Med.* **21**, 473–481 (2015).