The first child was diagnosed after birth and had the expected developmental delay associated with this disease. A sibling with the same disorder was diagnosed and treated prenatally, and had normal growth and development. Because it is not possible to know whether the second sibling would have developed normally without therapy, the effect of treatment from the presence of genetic modifiers in this individual cannot be determined.

If resilience on a genetic basis exists for a given genetic disease, the modifiers are almost certainly going to be gene- and disease-specific. Finding these will remain a challenge, regardless of how the individual case is recognized. But the degree of certainty with which these resilient individuals can be identified is critical.

To effectively deal with the confounders currently clouding this type of research, future studies need to ensure that the investigators have direct access to the patients to verify their clinical and genomic data. Self-reported data cannot address the nuanced way these conditions could be presenting, with variable expressivity or incomplete penetrance. In such studies, it is critical that all environmental factors that are potentially protective, such as treatment, be excluded.

A multifaceted approach should address the influence of modifier genes, environmental factors, allelic variation, epigenetics and gene–environment interactions. Both of the above examples illustrate the importance of being able to access the proband and related family for verification of the phenotypic and genotypic information. The traditional approach of looking for modifiers in extended families is still greatly underexploited. As comprehensive genetic testing becomes more common in medical care and in direct-to-consumer approaches, investigation of extended families will result in identification of additional resilient individuals.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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1. Chen, R. *et al. Nat. Biotechnol.* **34**, 531–538 (2016).
2. Rajabi, F., Waisbren, S. & Levy, H. Untreated phenylketonuria in adult sisters with discordant presentations of normal intelligence and intellectual disability. in *Society for Inherited Metabolic Disorders 39th Annual Meeting.* http://www.simd.org/Meetings/SIMD2016/Abstract/SIMD-Abstracts-2016.pdf (Elsevier, 2016).
3. Rosenblatt, D.S., Cooper, B.A., Schmutz, S.M., Zaleski, W.A. & Casey, R.E. *Lancet* **325**, 1127–1129 (1985).

# Regulation of synthetic biology under the Nagoya Protocol

**To the Editor:**
This December, representatives from 196 nations will come to Mexico for the 13th meeting of the Convention on Biological Diversity (CBD). During this meeting (known as 'COP 13'), the Parties to the CBD will focus on a critically important question surrounding synthetic biology: is the use of digital sequence information from genetic resources in foreign countries subject to the access and benefit-sharing requirements of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits from their Utilization? Resolution of this question may have far-reaching impacts for research and development in this area. And the answer may already be emerging as nations adopt and enforce new laws to govern access to and the use of genetic information.

**The Biodiversity Convention and its Protocols.** The CBD was opened for signature during the Earth Summit in 1992 and entered into force on 29 December 1993. To date, 196 countries have become Parties to the CBD; the United States has signed but not ratified the agreement. As its name implies, the purpose of the CBD is to conserve biological diversity and foster sustainable use of its components. However, the CBD also confirms an important principle of international law: each nation maintains sovereign rights over genetic resources occurring within its geopolitical borders.

During the past two decades, two Protocols have been adopted by the Parties to the CBD. In January 2000, the Parties approved the Cartagena Protocol on Biosafety. This Protocol seeks to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from biotechnology. To that end, the Protocol establishes procedures that allow countries to make informed decisions before agreeing to the import of LMOs into their territories.

More recently, the Parties adopted the Nagoya Protocol. It reaffirms each nation's sovereignty over its genetic resources and calls for the fair and equitable sharing of benefits arising out of the utilization of genetic materials. By ensuring benefit-sharing, the Protocol seeks to create incentives to conserve and sustainably use biodiversity. The Nagoya Protocol entered into force on 14 October 2014. To date, 88 countries have ratified or acceded to the agreement, and that number will likely reach 100 by the end of 2016.

**Access and benefit-sharing.** Under the Nagoya Protocol, any company or research organization seeking to use genetic resources must first obtain consent from the relevant foreign government authority and any indigenous community with jurisdiction over the resources. Genetic resources are broadly defined in the CBD to mean nonhuman "genetic material of actual or potential value." In exchange for gaining access to such materials, the user must agree to share benefits arising from utilization of the genetic resources. This *quid pro quo* is typically memorialized through an Access and Benefit-Sharing (ABS) agreement between the user and the foreign nation and/or community.

To establish an international system allowing for effective enforcement of these ABS requirements, the Nagoya Protocol obligates each Party to adopt provider measures and user measures. Provider measures are established by a source country to ensure that its genetic resources have been accessed based on mutually agreed-upon terms and with prior informed consent. User measures must ensure that genetic resources which are studied or commercialized in a particular nation were accessed in accordance with the provider measures of the source country. User measures may include mandatory due diligence reporting requirements and compliance checkpoints.

The CBD and Nagoya Protocol contemplate regulation of the physical transfer of tangible genetic or biological material from a provider country to a user, pursuant to an ABS agreement. New technologies emerging from synthetic biology fundamentally change that paradigm, however. The genome of a particular species may now be sequenced within a provider country and that

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information may be transferred digitally to a company or research entity for downloading to a DNA synthesizer. As a result, synthetic biology technologies beg the question of whether ABS requirements should apply to the use of digital sequence information from genetic resources.

**Global ABS deliberations concerning digital sequence information.** The Parties to the CBD considered regulation of synthetic biology during their 12th COP meeting in October 2014. There, they agreed to take a precautionary approach to the release of any LMOs resulting from synthetic biology under the Cartagena Protocol. At the same time, the Parties called for the formation of an *Ad Hoc* Technical Expert Group on Synthetic Biology (AHTEG) to evaluate, among other things, whether existing arrangements constituted a comprehensive regulatory framework for addressing potential impacts from synthetic biology technologies.

On the basis of information and comments received through an online forum established by the CBD, the AHTEG issued its report in September 2015. In its consideration of the potential adverse effects presented by synthetic biology technologies, the AHTEG noted that users may be gaining inappropriate access to the use of sequenced data without benefit-sharing under the Nagoya Protocol. That finding led the AHTEG to recommend that the Parties to the Nagoya Protocol should clarify the issue of digital genetic resource information as it relates to ABS.

In April, the AHTEG's findings were considered by the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA), the scientific advisory body that provides recommendations for further implementing the CBD. With respect to ABS regulation of digital sequence information, the SBSTTA was deeply divided on how to proceed. In the end, it issued a bracketed proposal calling for the CBD Parties to clarify whether and how the use of digital sequence information relates to ABS. This recommendation will be taken up at COP 13 later this year.

The application of ABS requirements to digital sequence information is being addressed under other international agreements, as well. The World Health Organisation (Geneva, Switzerland) is currently evaluating benefit-sharing requirements for genetic sequence data from pandemic viruses under the Pandemic Influenza Preparedness Framework. The UN Law of the Sea Convention is determining whether ABS provisions should govern digital information from marine genetic resources. The question is also being considered for plant genetic resources under the International Treaty on Plant Genetic Resources.

**Unilateral ABS efforts to regulate genetic information.** Although questions surrounding the use of digital sequence information may not be resolved at the international level for some time, this has not stopped countries from taking unilateral actions to regulate access to and use of information from their genetic resources. Indeed, the Nagoya Protocol only establishes an international floor for regulation of genetic resources, and it does not appear to preclude countries from restricting access to or requiring benefit-sharing for digital sequence information from genetic resources occurring within their borders.

One recent example of such unilateral action comes from Brazil. It adopted new ABS legislation in May 2015 to govern utilization of "information regarding the genetic origin of plant, animal or microbial species." The Philippines, another megadiverse nation, has recently declared that it will actively enforce its ABS restrictions governing the use of genetic resources for the "purposes of applying knowledge derived therefrom for commercial purposes." Similarly, Peru has recently stated that it will step up efforts to enforce its ABS requirements, which define genetic resources as "all biological material that contains genetic information of value of real or potential use." Other nations implementing ABS provisions will likely follow these examples, including Mexico, China and Malaysia, which have reportedly supported international efforts to regulate digital sequence information.

Although the United States has not signed or ratified the Nagoya Protocol, US companies and research organizations will nonetheless be subject to foreign ABS requirements governing access to and use of genetic information. Thus, if a US entity wishes to access genetic information in Brazil, it will need to comply with that country's new law and with any user measures that may potentially govern utilization of this information in particular jurisdictions. Moreover, for digital sequence information that has been deposited in public databases, researchers may need to ascertain, to the extent possible, whether foreign ABS requirements apply to use of these data.

**Conclusions**. As countries take steps to ratify and implement the Nagoya Protocol and as the question of international regulation of digital sequence information is considered at the international level, many nations may apply their own ABS requirements to the use of digital sequence information. This may be especially true when products developed through the use of synthetic biology technologies threaten to supplant or undercut traditional practices in the source country. Synthetic biology companies and research organizations should determine whether foreign ABS requirements may govern their use of genetic information. They should also closely follow developments at the international level later this year at COP 13. The consequences of not doing so may be severe and could result in patent invalidation, inability to study or commercialize a product, reputational harm and even criminal and/or civil penalties imposed by foreign governments.

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