

Gene sequences and biopiracy: Protecting benefit-sharing as synthetic biology changes access to genetic resources

by Edward Hammond

Synthetic biology is transforming access to genetic resources. While yesterday's biopirate hid seeds in his luggage, tomorrow's gene thief may smuggle her loot on a thumb drive or upload it to the cloud. With guidance from the Convention on Biological Diversity (CBD) and its Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, access and benefit-sharing (ABS) laws urgently need to adopt updated approaches to address this emerging reality, and public databases hosting genetic sequence data must be obliged to ensure that "open access" does not mean trampling on the rights of provider countries.

Technological transformation of access to genetic resources

Today, the easiest place to see the technological transformation currently underway is with the smallest organisms. In the health sector, cheap, deep and fast gene sequencing means that the full sequence of influenza viruses can be determined within hours of their isolation. And if that sequence is uploaded into an Internet database

or sent attached to an e-mail, gene synthesis technologies make it possible to recreate a living virus in under three days, at an appropriately equipped laboratory anywhere in the world.

In fact, today, some virus samples can be shared more quickly through the medium of digital sequence data than a physical sample – with an accompanying material transfer agreement – can be shipped across the world by courier. To put it concisely, digital access to some small organisms today is "Faster than FedEx."

And at the same time, the complexity of organisms (measured by the size of their genome) that can be synthesized from a digital sequence is increasing. Poliovirus, the first virus to be wholly synthesized in the lab, in 2002, is about 7,500 nucleotides long. Ten years later, in 2012, a 14,500-nucleotide influenza virus could be synthesized in under 72 hours (with the help of a technique called reverse genetics) – twice as long and far faster.

More recently, in November 2016, an American scientific team announced whole synthesis of adenovirus, with a genome of 34,000 nucleotides,

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more than two times the size of influenza and four and a half times that of poliovirus. And the Synthetic Yeast Genome Project, an international collaboration of several labs, plans to have synthesized the 16 chromosomes of *Saccharomyces cerevisiae* by the end of 2017 – a total of 12 million base pairs of DNA comprising an entire eukaryotic genome.

Of course, it is presently not possible to synthesize from scratch more complex organisms such as crop seeds and medicinal plants, but that may never be necessary. By combining sequence data with gene-editing technologies, such as CRISPR/Cas9, genetic diversity from one place can be introduced in organisms in another without physical access taking place, and without a material transfer agreement.

For example, corporate crop breeders interested in making tomatoes¹ more tolerant of salty conditions might turn their attention to the genetic sequences of tomato plants from the Galapagos Islands and coastal areas of Ecuador and Peru. With enough genetic data, they might identify mutations that make the plants salt-tolerant, from the digital sequences of these tomato plants. Gene-editing techniques can then be used to introduce those mutations into commercial cultivars for sale in North America or Europe.

Salt-tolerant tomatoes are merely a hypothetical example; the number of other traits in other crops that might similarly be accessed through data, and not physical transfer of materials, is practically infinite. Centres of diversity of crops and other species thus may unwittingly be allowing access to their genetic resources when gene sequences of their biodiversity are placed online without adequate controls.

Another example is genes that encode active compounds in medicinal plants, which could be used to manufacture pharmaceuticals. Rather than physically accessing the plant, a company might access the plant's sequence on an Internet database or via an e-mail from an allied researcher. The company may then adjust ("optimize") that sequence for expression in fermentable microbes and become able to manufacture the medicinal compound – all without ever physically accessing the source plant material, and without ever signing a material transfer agreement and making benefit-sharing commitments.

Notably, this means that exports of non-reproducing biodiversity samples for scientific research, e.g., "killed" or lyophilized plant tissue or microbial cultures, can effectively be the same as exporting viable organisms. If "dead" samples are sequenced and that data then used by synthetic biologists, entire microorganisms and/or key traits from more complex species can be brought back to life.

Arrival of ABS and genetic sequence data on the international agenda

The far-reaching impact of the combination of advanced sequencing and synthesis technologies, particularly CRISPR/Cas9, is simultaneously arriving on the agenda of at least three international discussions. Of these, the discussion of genetic sequence data (sometimes called "digital sequence data" or "digital sequence information") by the CBD is certainly the most important as it is the overarching agreement on biodiversity with which other efforts seek harmony and consistency.

While the implications of genetic sequence data have been informally discussed and anticipated for several years, the origin of the present discussion by the CBD is found in the report of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology,² which identified this important synthetic biology impact – "access without benefit-sharing" – on the Convention (p. 9).

The AHTEG's report was further discussed by the CBD's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) at its meeting in Montreal in April 2016.³ There, Northern delegations, particularly Japan, Canada and some European countries, launched an effort to derail the CBD's consideration of genetic sequence data by using a procedural argument – one that cloaks an intent to stop discussion of the issue altogether.

Despite the best efforts of those who did not want to see the issue considered further, Parties to the CBD which met in Cancun in December 2016 adopted a decision on sequence information of genetic resources that sets in motion a plan intended to lead to an important decision at their next meeting in 2018.⁴

The plan is a compromise that emerged after developing countries, concerned that the proliferation of sequences and other genetic information in the Internet “cloud” is promoting biopiracy, proposed that the Cancun meeting adopt a decision clarifying that sequence information should be treated equivalently to physical biodiversity samples for the purposes of benefit-sharing.

The process that results from the Cancun decision begins with a collection of views from Parties and the preparation of a fact-finding study. An AHTEG on Digital Sequence Information on Genetic Resources will then consider the results and report to the SBSTTA meeting in 2018. The SBSTTA then forwards its recommendations for consideration by the next Conference of the Parties (COP), which is scheduled to take place in late 2018 in Sharm el Sheikh, Egypt.

Among the issues that the AHTEG will consider is terminology. While the term “digital sequence information on genetic resources” is presently being used to describe the topic, several alternatives have been proposed and it is agreed that there is a need for clearer terminology around the issue. From developing countries’ perspective, that need includes being sure that the terminology used encompasses not only DNA and RNA sequences in various formats, but also amino acid (protein) sequences and other molecular information (e.g., DNA methylation), characterization data and natural information.

Terms of reference for the AHTEG also include examining “any potential implications of the use of digital sequence information on genetic resources for the three objectives of the Convention and the objective of the Nagoya Protocol and implementation to achieve these objectives.” The AHTEG will also identify the different types of sequence information that are relevant for consideration.

(The three CBD objectives are: conservation of biodiversity, sustainable utilization, and fair and equitable benefit-sharing. The Nagoya Protocol’s objective is fair and equitable sharing of benefits arising from the utilization of genetic resources.)

A corresponding decision passed by the COP serving as the Meeting of the Parties (COP-MOP) to the Nagoya Protocol implements a “coordinated approach” on the issue with the CBD, in this instance meaning that the Nagoya

Protocol may use the outputs of the study and AHTEG in its own work to implement benefit-sharing provisions.

Although there was disappointment over the focus on process, rather than substance, of the sequences issue, the decisions were widely welcomed as pointing the way towards the rapid decision that developing countries seek.

Consideration elsewhere: WHO and FAO

In addition to discussions at the CBD, the question of access and benefit-sharing and genetic sequence data for some specific circumstances is being discussed at the World Health Organization (WHO), and both the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) and the Commission on Genetic Resources for Food and Agriculture (CGRFA) of the Food and Agriculture Organization (FAO).

In the first case, because vaccine and other influenza viruses can be transmitted in the form of sequence data, WHO is considering how to implement the Pandemic Influenza Preparedness Framework (PIP Framework) in the face of this reality. Consideration of the issue by WHO has included attention to the terms of access to scientific databases, and consideration of if and how user access agreements to those databases might be used to ensure benefit-sharing.

The PIP Framework is an international access and benefit-sharing arrangement specific to potentially pandemic influenza viruses (and not all influenza viruses) and is the subject of the most advanced specific discussion of ABS issues at WHO. Member States of WHO, however, have noted that the Nagoya Protocol has wider potential relevance to human health, for example, access to samples of other pathogens and plant sources of medicines, and have commissioned a report on the Protocol.

Questions about ABS for genetic sequence data have also arisen in recent meetings of the Governing Body of the ITPGRFA. At its Sixth Session in 2015, the Governing Body referred the issue for consideration by the Ad Hoc Open-ended Working Group to Enhance the Functioning of the Multilateral System of Access and Benefit-sharing.

This Working Group, in turn, requested an information document on the issue, and the Co-Chairs provided a note that was considered at its March 2017 meeting. The Working Group agreed that the matter merits a thorough analysis by the Governing Body, at its Seventh Session. It stressed the need to cooperate with the CBD and the FAO Commission on Genetic Resources for Food and Agriculture, which itself is compiling information. The Commission at its meeting in January 2017 established a new work stream on “digital sequence information on GRFA” within its Multi-year Programme of Work and requested an exploratory fact-finding scoping study.

Ultimately, it is necessary that the approaches to ABS for sequence data that are taken by WHO, the ITPGRFA and the CGRFA be consistent with that of the CBD, the overarching agreement applicable to all biodiversity. The need to avoid inconsistent international treatment of access and benefit-sharing for sequences underscores the importance of the CBD taking up this issue quickly and effectively, to ensure that coherence is achieved between the different but related international processes.

Conclusion

Avoiding wholesale digital theft of genetic resources requires developing countries to overcome the economically motivated and self-interested positions of the Northern countries which seek to undermine CBD principles by delaying and derailing discussion of how to ensure that synthetic biology does not undermine 25 years of efforts to implement the CBD’s access and benefit-sharing provisions.

Stopping digital biopiracy is an issue that will continue to gain importance on the international agenda, particularly at the CBD, and it is important that the CBD’s discussion advances quickly, so that developing countries’ rights are not harmed by more years of “open” sharing of genetic sequence data in ways that are irresponsible towards provider countries and provider peoples.

Early discussions among experts suggest that much more careful attention must be paid to data access agreements at online databases, including so-called “open access” databases. Creating more specific user agreements with legally binding access and benefit-sharing stipulations may be necessary in order to prevent a digital

DNA “darkweb” where genetic resources are distributed and claimed in violation of access and benefit-sharing principles and rules.

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Endnotes

1. Tomatoes are not among the crops listed in Annex 1 of the International Treaty on Plant Genetic Resources for Food and Agriculture; thus, access and benefit-sharing for the crop falls under the CBD.
2. UNEP/CBD/SYNBIO/AHTEG/2015/1/3
3. A more detailed account of the SBSTTA’s discussion may be found at: Hammond E 2016. Synthetic biology debate ahead of biodiversity treaty’s top meeting. TWN Information Service on Biodiversity and Traditional Knowledge, 6 May. URL: <http://www.twn.my/title2/biotk/2016/btk160502.htm>
4. A more detailed account of the Cancun discussion may be found at: Hammond E 2016. Biodiversity Convention adopts plan for benefit sharing for genetic sequences. TWN Information Service on Biodiversity and Traditional Knowledge, 19 December. URL: <http://www.twn.my/title2/biotk/2016/btk161208.htm>