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Sharing Pathogen Sequence Data for Global Scientific Research under the Nagoya Protocol to the Convention on Biological Diversity

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13.1 TENSIONS CONCERNING THE COVERAGE OF GENETIC SEQUENCE DATA UNDER THE CONVENTION ON BIOLOGICAL DIVERSITY

The Convention on Biological Diversity (CBD)[1] may be characterized as a response by low- and middle-income countries (LMICs) to a preexisting state of inequality with regard to the development and commercialization of products deriving from the access to and use of biological diversity in nation states. Historically, scientists from the more economically developed countries, while exploring the genetic resources in LMICs, would help themselves both to physical specimens from plants, animals, and microbiological materials and to traditional knowledge (TK) of indigenous populations about how to make economical use of such resources and knowledge. One needs to recognize that the CBD was a concerted effort to invalidate such practices and, instead, to assert sovereign ownership over both local genetic resources and TK as well as a fair share of any economic benefits arising from their commercial applications. The adopted Nagoya Protocol[2] to the CBD then supplied strong enforcement measures to implement new remedies to the old inequalities that the CBD sought to rectify.

[1] The CBD is a multilateral treaty adopted under the United Nations on June 5, 1992, and entered into force on December 29, 1993. Its objective is to develop national strategies for the conservation and sustainable use of biological diversity. It is generally seen as the key document regarding sustainable development.

[2] The Nagoya Protocol to the Convention on Biological Diversity on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization is a supplementary agreement to the CBD that aims to implement one of the three objectives: the fair and equitable sharing of benefits arising out of the utilization of genetic resources. The protocol was adopted on October 29, 2010, and entered into force on October 12, 2014.

This chapter does not question the policy decisions embodied in the CBD and its Nagoya Protocol to eliminate practices rooted in the preexisting state of inequality. By the same token, we emphasize the importance of scientific research and TK as a potential source of major benefits to all humanity. In this context, the current debate about access to genetic sequence data (GSD) must be considered. There is no going back on the foundational obligations of the CBD concerning negotiated access to genetic resources and the data resulting from their study and applications, including the relevant TK of indigenous populations. Nevertheless, it must be made clear that neither the CBD nor the Nagoya Protocol will be allowed to interfere with basic scientific research so long as the relevant genetic resources were obtained in the first instance by modalities sanctioned under the treaties in question. These modalities, in turn, support basic scientific research without undermining the rights of provider countries to a fair share of any benefits resulting from commercial applications of such scientific research based on specific genetic resources and TK obtained from those countries. The rest of this chapter explains how to reconcile these tensions in the specific case of GSD, using pathogen research data as an example.

Preserving the Earth's biodiversity is essential to human survival and a major factor in global economic development (Kolbert, 2014). Research on the components of biodiversity, especially genetic resources, not only enables scientists to discover and understand their characteristics and promote needed conservation but also contributes to the development of innovative products and applications while bolstering efforts to strengthen public health, among other goals (Halewood et al., 2012; Ribeiro et al., 2018b).

Conservation and management of the Earth's biodiversity include manifold stakeholders that range from LMICs to the most developed countries, along with not-for-profit organizations, industries, scientists, and local indigenous communities (Access and Benefit-Sharing Clearing-House, n.d.; Aoki, 2008; Jeffery, 2004). The divergent views of these stakeholders with respect to the proper treatment of genetic resources and GSD – now designated as "digital sequence information" (DSI) for purposes of current negotiations (Morgera et al., 2019) – typically depend on whether they regard themselves primarily as potential providers or users of genetic resources (AHTEG, 2019).

These views reflect different approaches to rights and obligations concerning the management of such resources. More economically developed nations, the primary users and exploiters of resources for for-profit and nonprofit goals, mostly promote open exchanges of data, materials, and knowledge to achieve public benefits. LMICs, which often possess the most diverse and rich biodiversity resources, position themselves as provider countries seeking to restrict access in order to effectively claim a fair share of revenues and overall commercial benefits (Morgera et al., 2019). It is important, however, to point out that in accessing and using genetic resources, today's providers might, and in many cases will, become

users in time, just as some users may eventually become providers (Rohden and Scholz, 2021).[3]

To support sustainability and fairness in the management of biodiversity, the CBD expresses the following objectives: (1) the conservation of biological diversity, (2) the sustainable use of its important components, and (3) the fair and equitable sharing of benefits arising from the utilization of genetic resources (preamble, arts. 2, 8, 15–16). The Conference of the Parties to the CBD (COP) later developed the Nagoya Protocol in 2010 to further regulate access to genetic resources regarding the sharing of benefits. This legal framework subjects all users of plant, microbial, and animal genetic resources to national legal requirements of prior informed consent (PIC), mutually agreed terms (MAT), and access and benefit-sharing (ABS) agreements. A primary objective of the Nagoya Protocol is to enable member states as providers of genetic resources to share monetary and nonmonetary benefits derived from using such resources (arts. 3–5; Curci, 2010).

What seems clear in recent years is that the CBD, as bolstered by its Protocol on enforcement measures, can undermine scientific research on planetary biodiversity. A clear impediment to science that merits particular attention is the growing difficulty of complying with varying national ABS measures for conducting both *in situ* and *ex situ* not-for-profit research that requires access to, or some uses of, genetic resources (Sett et al., 2022). This impediment can affect ethically conducted bioprospecting as well as the collection of fundamental research data that serve primary societal needs, including critical health interventions, whether focused on human, animal, or plant life that require scientifically valid evidence to determine the best course of action (Bhatti et al., 2009; Scutchfield and Lamberth, 2010).

In the specific domain of public health, restrictions on access to and use of GSD can have serious adverse effects on not only upstream public health measures but also follow-on research for innovation and applications, such as the development of diagnostics, therapeutics, and vaccines, which are essential for the containment of cross-border epidemics and the spread of disease generally (National Research Council, 2009; WHO, 2005).[4] The role of GSD in public health surveillance and response continues to grow in importance (WHO, 2019), yet the willingness of countries to share such resources and, especially, related data has palpably diminished, despite the emphasis on the equitable sharing of benefits under the Nagoya Protocol. Epidemics – such as MERS, Ebola, ZIKA, and most recently COVID-19 – have emerged since the Protocol was adopted, during which countries refused to

[3] This study showed that (1) the main users of the public databases of the International Nucleotide Sequence Database Collaboration – the United States and China – are also the main providers, (2) every country around the world has database users, and (3) users typically sample and use GSD from their own country much more than from abroad.

[4] There are very substantial research and health aspects of regulating planetary biodiversity and maintaining open access to genetic materials and related data that need to be preserved.

rapidly share pathogen materials or sequences owing to countervailing concerns about the need to defend ownership and the sovereign rights of provider states (Halabi, 2019; Peeling et al., 2020; Pisani et al., 2018; Sett et al., 2022).

The CBD and its Nagoya Protocol have further contributed to this tension. PIC, MAT, and ABS conditions can conflict with international guidelines or other sharing obligations, such as those of the International Health Regulations of the World Health Organization (WHO), the International Covenant on Economic, Social and Cultural Rights (Aarestrup and Koopmans, 2016),[5] or even the Declaration on the TRIPS Agreement and Public Health (Abbott and Reichman, 2007). For example, the impetus given to parties to the CBD under Article 8(b) of the Nagoya Protocol with respect to the rapid sharing of genetic resources in health emergencies insufficiently recognizes the constraints on related ABS obligations otherwise imposed from two directions. First, other treaties, such as the International Health Regulations, demand that each country promptly share critical information, including scientific data – and arguably GSD – which is now crucial in determining public health risks and possible countermeasures to address infectious disease outbreaks. Second, global efforts to address serious health threats will, in many cases, entail research on the nature of pathogens and on the collective international sharing of critical data derived from pathogen genetic resources that domestic ABS laws may now regulate.

It thus seems a complex task to develop a one-size-fits-all solution to this problem of conflicting interests that would address the concerns and needs of all stakeholders, all subject matter fields, and all disciplines involved. The complexity of managing tangible or intangible assets, such as GSD, constitutes additional challenges to the evolving task of reconciling the legal obligations under the CBD with the needs of global public health (Buck and Hamilton, 2011). Nonetheless, the COP needs a coherent approach to scientific information in general and GSD in particular to avoid potential barriers to research and burdensome (re)negotiation of legal texts to cover major new scientific tools, discoveries, and their implications.

Public health interventions during outbreaks and epidemics are time-sensitive, and delays in access to pathogenic materials and GSD can conflict with the moral imperative to save lives through the prevention of and response to public health threats (Ribeiro et al., 2018a; WHO, 2019).[6] Because pathogens and, to a still unknown extent, related data are considered genetic resources within the CBD, they are potentially subject to the Nagoya Protocol's robust enforcement measures and the resulting legal problems (Bagley, 2016).

[5] See Articles 12 and 27 of the International Covenant on Economic, Social and Cultural Rights for collaboration to recognize the right of everyone to the highest standard of prevention, treatment and control of epidemic, endemic, occupational, and other diseases.

[6] The authors recognize that both plants and animals are also covered by the CBD, although they are often less data-intensive than the field of microbiology.

Although the CBD and the Nagoya Protocol have as one of their core goals to enhance fairness in the sharing of benefits arising from the use of genetic resources, their negative impact on public health research and response can reinforce inequalities in outbreak preparedness and response capacity. Epidemics commonly emerge in many LMICs through zoonotic spillovers due to the proximity of humans, livestock, and wildlife. Because of weaker public health systems and a lack of sufficient response capacity, these countries are usually the ones most affected and take longer to recover from the devastating impact of epidemics (WHO, 2018b). The global and rapid sharing of pathogen materials and data and international collaboration for developing pharmaceutical and nonpharmaceutical countermeasures help affected countries to control and mitigate disease within their borders and the rest of the world to prevent and control the spread of the epidemic. As the world faces increasing infectious disease threats with global impacts, solidarity and collaboration are more important than ever to address critical policy, operational, and capacity barriers ahead of an emergency.

Accordingly, this chapter focuses on how to conform ABS practices to pathogens and related GSD, independently of how coverage is ultimately defined under the CBD. In so doing, the authors draw attention to the obstacles that compliance with the CBD might otherwise have on biodiversity research in general and on pathogens and infectious diseases in particular. The authors further examine the real-world consequences of their proposal for global public health initiatives, with particular attention to sharing practices already adopted in the public health field that enable the free exchange of genetic materials and, increasingly, of related data for research purposes.[7]

13.2 THE DISRUPTIVE COMPLEXITY OF GENETIC SEQUENCE DATA

The COP must recognize and suitably resolve the rapidly evolving tensions that scientific research and technologies continue to generate for implementing the Nagoya Protocol's legal framework. Complex legal problems also arise from the growing importance of GSD in scientific research generally and public health in particular, and especially from mounting pressures on originators to make such data freely available for follow-on research and development (Morgera et al., 2019; National Academies of Sciences, Engineering, and Medicine, 2021; Reichman and Uhlir, 2003).

On the one hand, when GSD are traceable to specific genetic resources and their providers, a case for coverage by the CBD can more readily be made. On the other hand, to the extent that open access to GSD enables scientists to recreate, say,

[7] National Research Council (2009) stressed the potential impact on public health, research, and applications of maintaining open access to genetic materials and related data generally within the context of regulating planetary biodiversity.

viruses and enhance their functions, it could make the need to access and use biological samples (physical materials) less acute or eventually even obsolete, to the detriment of those otherwise entitled to benefit-sharing obligations under the Nagoya Protocol.[8]

Article 2 of the CBD expressly applies to genetic resources and "other elements of heredity" (Schei and Tvedt, 2010). The question of whether this clause implicitly covers GSD or not depends, in the first instance, on how the term is defined, as well as on the scope of the textual language adopted by the Nagoya Protocol. There is, however, no agreed definition of GSD for this purpose, nor was there any agreement on the status of the current replacement descriptor, that is, DSI, apart from thornier questions about the extent to which the CBD covers GSD at all (COP, 2016: preamble; Houssen et al., 2020).

By the time of the fourteenth CBD-COP meeting in 2018, the term DSI had been adopted as a placeholder for GSD, and a study on the concept and scope of DSI, including its then-current usage, was formally requested in the absence of any consensus.[9] Against this background, major decisions were made in March 2020, when the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources (AHTEG) adopted a surprisingly broad and coherent set of definitions in its report (AHTEG, 2020b). The experts successfully classified relevant "genetic and biochemical information" into three broad categories that are conceptually cumulative – namely (1) Group 1, covering "DNA and RNA"; (2) Group 2, covering "proteins and epigenetic modifications" plus the contents of Group 1; and Group 3, covering "metabolites and other macromolecules" plus the combined contents of Groups 1 and 2 (AHTEG, 2020b: annex 1, 9 tbl.1).

The avowed object of this report was to advise the Open-Ended Working Group on the Post-2020 Global Biodiversity Framework.[10] The AHTEG accordingly concluded with the recognition that measures governing ABS in compliance with the CBD might need to vary within the three main groupings of DSI. In so doing, AHTEG deliberately avoids recommendations about how DSI should ultimately be

[8] Third World Network (2019) described the case of the pharmaceutical company Regeneron that used GSD of a Guinean Ebola virus collected in 2014 to create a treatment. To make the drug, Regeneron downloaded the Guinean GSD from GenBank, which was made available by the German Nocht Institute. By downloading the GSD from GenBank and then synthesizing it, rather than requesting a virus sample from Nocht, Regeneron did not sign an MTA requiring negotiation of a benefit-sharing agreement. Therefore, the company is arguably manufacturing a product without complying with the binding obligations for benefit sharing with Africa and Guinea.

[9] For the decision of the COP serving as the meeting of the Parties to the Protocol (COP-MOP) in 2018 to establish an Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources and an invitation to parties and stakeholders to submit views and information about how the CBD should cover DSI, see AHTEG (2021). Altogether four peer-reviewed studies on DSI were commissioned during the 2019–21 inter-sessional period, with the first focused on the concept and scope of DSI itself (AHTEG, 2020a).

[10] Established by the COP under Decision 14.34.

governed for purposes of compliance with the CBD, which was not its mission.[11] What it has clarified is the definitional confusion surrounding DSI/GSD in previous discussions so that the COP should better understand what it is dealing with.

Meanwhile, the term DSI is perceived as comprising a broad range of matter subject to interpretation (i.e., DNA sequences and derivatives, but not subsidiary information). In contrast, GSD had acquired a narrower scope in CBD discussions, typically limited to nucleotide sequence data (DNA and RNA) in closer proximity to material genetic resources (Houssen et al., 2020; WHO, 2011).[12] That proximity, in turn, makes it easier to accurately identify or infer the genetic resource from which the relevant data in question were derived for purposes of ABS applications. Because the term GSD thus lends itself to a narrower, more workable subject matter concept for legal interpretation, GSD throughout this chapter is used as a counterweight to the possibly broader notion of DSI.

Enforcing ABS obligations under the CBD, however, depends largely on the ability or inability to monitor the uses of any specific genetic resources and on maintaining control over the chain of custody. Because the authors assume that GSD/DSI will likely become reachable under the CBD in many, if not most, cases, the deeper substantive issues will depend on the consequences of such coverage.

Meanwhile, context and comparison give GSD their actual value through comparing sequences on a large scale combined with the application of knowledge gained from scientific research in an iterative fashion (Rohden and Scholz, 2021). This process is made possible through comprehensive virtual libraries, such as the open-access databases of the International Nucleotide Sequence Database Collaboration (INSDC).[13] At the same time, the huge volume and constant growth of publicly available genetic sequences constitute a clear obstacle to any attempt to monitor all transactions involved in accessing and using any given set of GSD. Once GSD are shared in open-access repositories, it is not always clear – and therefore very hard – to monitor how they will be used in the future (Laird and Wynberg, 2018).

For example, genetic sequences accessed for academic research purposes that are subsequently uploaded onto public databases may eventually be used commercially

[11] The AHTEG report nonetheless notes possible approaches, including "flat-fee access with benefit-sharing triggered by utilization or commercialization and/or a possible multilateral approach."

[12] WHO's view on "the order of nucleotides found in a molecule of DNA or RNA" is that they contain the genetic information that determines the biological characteristics of an organism or a virus. This definition clarifies the extent of what is included as only DNA/RNA, thus excluding proteins, metabolites, and metadata associated with the genetic resource.

[13] The INSDC (www.insdc.org) consists of a longstanding foundational joint effort to collect and disseminate databases containing DNA and RNA sequences. It involves the following computerized databases: the National Institute of Genetics's DNA Data Bank of Japan, the National Center for Biotechnology Information's GenBank in the United States, and the European Molecular Biology Laboratory–European Bioinformatics Institute's European Nucleotide Archive. All of the data in INSDC is available for free and have unrestricted access, for any purpose, with no restrictions on analysis, redistribution, or re-publication of the data.

by many different actors without the original providers becoming even aware of or involved in the process. Other potential loopholes in the ABS framework could arise when commercial firms only use specified GSD for full product development, whether by bioengineering or for testing products. While even legitimate bioprospecting could trigger some ABS obligations under the CBD, the firms in question might partner with academic institutes or laboratories to test the resulting products under a "noncommercial" umbrella, thus delaying if not concealing legal liability.[14] Moreover, once private-sector entities acquire GSD from open-access repositories, they might have little incentive to disclose potential benefits to distant providers (Gostin et al., 2017).

While further work on tracking and tracing genetic sequences may help engender trust, another complicating factor is that GSD acquires an intermediate scientific status over time, in the sense that component sequences may be used in an ever-expanding variety of scientific research projects. As a result, questions of ownership and property rights – if not unknown or unknowable – may inhibit further basic research projects and commercial innovations (Flach et al., 2019; Rohden and Scholz, 2021).[15]

Consider, for example, that networks of researchers from diverse institutional or sectoral affiliations – industry, government, academia, and the laboratories of all sectors – may span the globe in the process of collaborative innovation. In such cases, users may add incremental value by providing data and knowledge along a chain that involves "swift compilation, comparison and reanalysis of genetic information from a variety of sources, across multiple databases and gene sequences."[16] Genetic materials from diverse organisms originating from different habitats around the world are thus often combined in developing new products, processes, and technologies. The result may well depend on a derivative sequence that reflects an "average" of all the various input sequences, thus making it virtually impossible to determine the relative value of each component sequence as part of the ultimate ensemble (Laird and Wynberg, 2018).

Synthetic or modified GSD may also be created from long-standing, publicly available sequences, many of which may not have recorded links to the original

[14] WHO (2018a: annex 3) discussed ABS under the Pandemic Influenza Preparedness Framework.

[15] Given large-scale meta-analysis projects involving big data analysis, the information from many studies and experiments may be collected and analyzed together. Moreover, many new bioinformatics tools and biological databases are built by developing new algorithms and scientific approaches and subsequently mining public databases for existing knowledge, as well as performing new bioinformatic analysis.

[16] Laird and Wynberg (2018) provide an example, mentioned by the International Chamber of Commerce, on the development of a new consensus phytase to improve the nutritional value of animal feed: "[I]n state-of-the-art bioinformatics projects, hundreds of thousands of (amino acid or nucleic acid) sequences may be used to develop a particular commercial product. The final product has a sequence that represents an 'average' of all input sequences; as a result, it is virtually impossible to determine the relative value of each individual input sequence."

genetic resource or country of origin. This factor complicates how benefit-sharing should attach to GSD/DSI over time under the CBD. One study asks "whether there is ever a point where the original genetic material has passed through so many stages of transformation that ABS requirements attached to the original material no longer apply?" (Reichman et al., 2015).

Commercial applications of GSD are thus so varied and so rapidly evolving that it becomes extremely difficult, if not impossible, to characterize with any certainty the utilization of specific sequences or estimate their commercial value. Even when GSD contribute to developing a given commercial product, they may also be used to develop other industrial processes, research tools, or improved technologies that are not sold and may be freely shared (Laird and Wynberg, 2018; Rohden and Scholz, 2021). These complex arrangements cast further doubt on the ability to attribute shared benefits to any single country or provider, especially when relevant data are easily accessed or processed for further utilization irrespective of the territorial boundaries where genetic resources may have originated.

Given the added value of open-access databases and the fact that there is no way to predict whether any specific genetic sequence components may prove useful in research and product development, broader availability ought to be favored whenever feasible, especially in view of their widening use to support many important societal needs (Ribeiro et al., 2018a). Impeding the flow and use of such information would significantly undermine research projects in diverse fields, including those that contribute to the specific objectives of the CBD and the Nagoya Protocol. The importance of GSD for global public health as an essential tool for disease surveillance, investigation, source-tracing, and the development of medical countermeasures further supports the case for the free availability of such a socially beneficial resource.

13.3 CODIFYING MULTILATERAL COMPLIANCE MEASURES FOR UPSTREAM GSD

This chapter contends that a relatively acceptable solution is attainable once the parties shift the focus of attention away from the "coverage" issues and directly address the consequences of potential ABS coverage of GSD. If a satisfactory compromise concerning the scope of protection and the modality of implementation can thus be found, it would help diffuse the pressure hitherto concentrated on definitions and eligibility.

13.3.1 *The Basic Proposal*

The freedom to access and use genetic resources for global public health purposes, once confirmed by the COP, must accordingly be coupled with a corresponding duty to share proceeds from the results with the country or countries providing genetic materials – in this case, any pathogens at issue. An obligation to this effect

must thus be embodied in any waiver for research purposes adopted by the parties to the CBD. Such a waiver should free scientific researchers from negotiating access and usage at the upstream, noncommercial research stage but not from the duty to report and share proceeds from all downstream commercial applications.

Ideally, any solution to the problems of conforming potential uses of pathogen GSD to the CBD requirements would ultimately be embodied in a multilateral agreement applicable to all the member states. Such a regime should incorporate a waiver of PIC and MAT for noncommercial scientific access and uses. Benefit-sharing terms would nonetheless be triggered when, and only if, commercial applications are envisioned using a "change of intent" clause that expressly guarantees compliance with the CBD's benefit-sharing obligations.

From a purely legal perspective, the legitimacy of such an initiative would follow from Articles 4 and 8 of the Nagoya Protocol. Article 4 validates multilateral arrangements for facilitated access to genetic resources for research and applications, which would override the need to bargain directly with national governments in every case, as otherwise required under Article 8 (Reichman et al., 2015). A multilateral framework adopted to facilitate scientific research would thus be necessary to bring any given project within the scope of Article 4. Once codified by the COP, any standard-form waiver favoring pathogen research that covered specific projects should thereafter suffice (Reichman, 2018).

To implement such a waiver, Standard Material Transfer Agreements (SMTAs) authorizing noncommercial research under the CBD should likewise embody a "change of intent" clause and define how that clause should apply to specific collaborative ventures (Reichman, 2018; Ribeiro et al., 2018a). In principle, parties to these SMTAs would not need to expressly prohibit commercial use of public-research results, whether by private-sector or public-research entities. Instead, when applicable, drafters of both bioprospecting contracts and SMTAs to be covered by the proposed waiver should consider expressly allowing eventual commercial applications with some built-in equitable sharing of revenues if and when they are generated. Correctly devised and implemented "change of intent" clauses could thus help to stimulate both research and commercial applications.

Compliance measures of this kind could thus be validated a priori under either an amendment to the CBD or a waiver embodied in a multilateral Memorandum of Understanding (MoU) to be devised expressly for pathogen genetic resources with the collaboration and endorsement of relevant international organizations. If the global public health community were to take the lead, the proposed waiver for GSD would logically be developed by the WHO, with inputs from the microbiological community as represented by the World Federation of Culture Collections (WFCC).[17] Such an MoU would necessarily impose its waiver for noncommercial research purposes

[17] See Microbial Resource Research Infrastructure (MIRRI), www.mirri.org/about/. The WFCC has already developed an SMTA for nonprofit research on genetic materials.

allowing unrestricted access to both pathogen materials and related data, including GSD. By the same token, the WFCC and the INSDC could conform to their standard sharing practices (Rohden and Scholz, 2021), through SMTAs, notification of terms and conditions, or other access agreements. Additionally, they could provide links between the available resources and the legal (ABS) conditions of use for commercial applications, thereby acknowledging the proposed waiver for noncommercial research purposes.

In the long run, however, an MoU regulating pathogen sharing should serve as a steppingstone to a broader, more comprehensive waiver favoring noncommercial research access and use of all GSD and potentially other genetic resources – plant, animal, and microbial – under the CBD as a whole. Such a general waiver would have to be adopted by the COP. Once adopted, the resulting "change of intent" clauses to be embodied in SMTAs should enable local researchers to freely engage in international collaborations, as long as they are covered by the terms and conditions in the standard agreements.

The efficacy of such a regime would depend in part on the successful development of the tracking system under consideration at the World Intellectual Property Organization (WIPO), the WFCC, and INSDC (Bagley, 2016).[18] It is worth noticing, moreover, that microbes already cannot legally be exchanged for any research purposes without bearing unique identifiers that must be cited in all relevant publications (Reichman et al., 2015). The eventual ability of researchers to file SMTAs with the ABS Clearing House to be established under Article 14 of the Nagoya Protocol could then make it unnecessary for researchers engaged in international collaborations to notify their respective governments, so long as binding standard PIC, MAT, and ABS terms were embodied in the relevant SMTAs.

If the CBD's COP or the WHO eventually decided to establish a consortium for purposes of exploiting pathogens and GSD on a globally regulated basis, they could also adopt a liability rule – that is, a "take and pay" rule – for commercial applications of GSD taken from the commons (or semi-commons, as the case may be) (Calabresi and Melamed, 2018; Reichman and Lewis, 2005). In assessing payment options, moreover, it seems worthwhile to consider the methods already adopted for such a purpose by the multilateral regime governing the Crop Commons, as established under the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) in 2001 (Reichman et al., 2015). This approach entails a built-in "take and pay" rule for plant cultivars taken from the Crop Commons by commercial plant breeders. Suppose a similar scheme were to be adopted by the proposed multilateral regime to cover GSD under the CBD. In such a case, a liability rule could then require payment of a small percentage of any future

[18] Whether WIPO will succeed in developing a tracking system for some or all genetic resources and related data remains to be seen.

commercial revenues back to the CBD's commons to support the costs of the sharing enterprise.

Under this approach, a percentage of any commercial revenues stipulated ex ante must be paid either to the provider country when known or to the General Fund of the CBD under Article 10 of the Nagoya Protocol, if undetermined. Smaller access charges could also be required to support the costs of any global public repositories to be devised for GSD under pending proposals. As matters stand, the CBD already requires firms undertaking commercial applications to engage in prior benefit-sharing negotiations (bilaterally) with countries that provide relevant genetic resources or with other designated authorities covered by the treaty in certain cases. Under the aforementioned proposal, the obligation to share benefits with provider countries would instead be expressly incorporated into the waiver to be adopted by the multilateral regime for this purpose.

13.3.2 *Further Implications of the Proposed Waiver*

One persuasive argument for a codified waiver allowing research access and uses of pathogen GSD is that the concomitant obligation to share any proceeds from commercial applications would likely yield more monetary benefits for CBD countries that possess relevant genetic resources over time than any policy that otherwise restricted upstream scientific research. That realization should, in turn, make provider countries more willing to allow bioprospecting under the proposed waiver for research uses than at present. A case can also be made that such a waiver should lead to more nonmonetary societal benefits for all CBD member states in the form of better public health outcomes and more innovation. So, in the spirit of the CBD enhancing fairness in the utilization of genetic resources, such a multilateral system can also raise more funds to address inequalities in research capacity and strengthen public health response efforts.

Transnational collaborations to support responses to outbreaks also illustrate how the timely sharing of pathogen genetic resources benefits society, irrespective of whether they originated from provider or user countries. Experience with regard to the 2013–16 Ebola outbreak in West Africa supports this thesis. During that crisis, gaps in the sharing of viral samples and (meta)data, coupled with delays in the public release of GSD, led to speculation about the sources of infection, the possibilities of diagnosing the infection with available assays, and possible mutations over time that increased transmissibility (Dudas et al., 2017; Ribeiro et al., 2018b). Although at later stages of that outbreak, the near real-time sequencing of strains did finally provide essential information directly to public health officials, the suboptimal sharing of data throughout the outbreak eventually allowed the virus to spread to other countries in the region and evolve into a global health crisis.

It is also worth noting that the measures proposed in this chapter would not necessarily exclude other ancillary approaches. For example, even if global

repositories for sharing pathogen GSD were eventually established, the contractual waiver proposed earlier in this chapter would remain viable and important in keeping with the goals of the CBD. Consider, for example, that the mere existence of publicly available repositories would not ensure that all relevant data would end up in such repositories (apart from the definitional issues concerning the scope of GSD/DSI discussed earlier) (Ribeiro et al., 2018a). A globally adopted waiver under the auspices of the CBD would, instead, apply to all relevant uses of pathogen data and materials, whether or not stored in public repositories, and the implementing instrument should expressly prohibit SMTAs from overriding the proposed waiver by contract.

In other words, once embodied within the CBD and its Nagoya Protocol, the waiver would become useful in every case. At the same time, any pooling of relevant repositories under the CBD, if successful, would further enhance the global scientific infrastructure. However, the willingness of biodiversity-rich countries to accept such a built-in waiver cannot be taken for granted. Besides concerns about enforceability, their participation may depend on estimates of the nonmonetary benefits likely to flow from open-data sharing and on the misconception that all genetic resources are likely to generate revenues for benefit-sharing purposes (Reichman et al., 2015).

In this context, the prospect of greater access to public databases (and possibly related technology) may seem to be an insufficient incentive to potential providers, especially if biodiversity-rich countries lack adequate molecular research capacity or biotechnology infrastructure to make domestic use of any resulting global repositories. The prospect of shipping samples abroad for sequencing is also an enduring concern for local governments that fear losing control over genetic resources whose data could easily be loaded into public databases. There have been cases, for instance, where samples initially shared for purposes of analysis were later presented at international meetings without advance notification or attribution to providers as authors (Sedyaningsih et al., 2008).

To address these remaining inequalities, rather than restricting access based on bilateral benefit sharing, a situation that is likely to be technically and logistically infeasible and would only benefit a few, a multilateral system for GSD would generate more access, use, and therefore benefits. These monetary and nonmonetary benefits could be directed to capacity-building initiatives in developing countries, such as bioinformatics training, building data infrastructures, and developing and providing data-analytical tools.

Still, it remains true that big companies and well-endowed research institutions may sometimes profit more from open-access policies and an expanding public domain than smaller competitors. For example, big players may find it easier to file patent applications on genetic markers, targets, specific genotypes, and the like (disregarding variations by country in what qualifies as patentable subject matter) (Bagley, 2016). Meanwhile, smaller enterprises that lack such capacity may be

locked out.[19] Nevertheless, since such unequal opportunities are built into any competitive economic system, they constitute a fact of life that the COP cannot fully resolve.

One way around this problem is through the formation of a patent-holding consortium, whereby each contributor to the knowledge valorization process, including providers of genetic resources, researchers, and both large and small enterprises, are rewarded with a share of any funds arising from the resulting property rights (Simon et al., 2005). Such a de facto patent pool could become a recognized component of ABS obligations under the CBD as a form of monetary benefit sharing. Moreover, properly devised "change of intent" clauses would further enable provider countries to benefit from foreign patents by means of built-in sharing conditions applicable to patents, patent pools, or other monetary sources.

To date, very few examples exist of patent pools during epidemics (Simon et al., 2005). In May 2020, the WHO launched the COVID-19 Technology Access Pool (C-TAP) for developers of COVID-19 therapeutics, diagnostics, vaccines, and other health products to share their intellectual property through nonexclusive licenses in a patent pool. Nevertheless, the C-TAP failed to engage the major vaccine developers, which resulted in inequality in access to vaccines in developing countries (Van de Pas et al., 2022). This means that for such mechanisms to work during a crisis, they need to be embedded in a structured, democratic, multilateral governance framework and not dependent on political willingness and pressure during a crisis, guided mainly by narrow national interests.

In any event, steps should be taken to ensure that commercial entities identifiable by their Internet URLs are not excluded a priori from accessing and using pathogen GSD covered by the proposed waiver. A treaty-based waiver for pathogen genetic resources, including GSD, must recognize that "noncommercial" refers to the nature of the use and not the users. Commercial entities, not-for-profit organizations, and academic institutes should be allowed to use GSD for noncommercial research purposes. In contrast, their actual undertaking of commercial applications should always trigger the duty to pay reasonable royalties under the GSD waiver and the corresponding "change of intent" clause.

As regards the modality of implementing monetary obligations for both the commercial use of pathogen resources and funding for the multilateral system, as noted earlier, we endorse a built-in "take and pay" rule (i.e., "liability rule") under which a small percentage of any commercial revenues stipulated ex ante must be paid either to the provider country or to a General Fund when that country remains unknown. In so doing, the COP might well consider that a simple set of standardized royalty obligations, like those of the ITPGRFA, would engender more upstream

[19] See The Cambia Bios Initiative – Supporting Rationale, https://cambia.org/bios-landing/the-cambia-bios-initiative/.

uses of GSD, which in the long run might create more likelihood for commercial revenues to be shared under the CBD.

One must recognize that some stakeholders may still cling to the notion that all uses of GSD should require prior negotiation on ABS. The fallacy of such a position is that neither side can accurately predict which products or revenues, if any, would ever result from upstream scientific research (Reichman et al., 2015). Moreover, an *ex ante* liability rule would significantly lower transaction costs for all relevant parties and clarify potential risks and costs for commercial entities when engaging in product development.

Will the CBD countries insist on some advance payment even for noncommercial or potentially commercial research using pathogenic resources? As previously noted, a relatively small "user's fee" might become tenable when pathogen GSD are taken from a global commons or semi-commons, as the case may be, because such fees would help defray the costs of upkeep for the repositories in question (Reichman et al., 2015). Absent such an approach, the idea of charging substantial amounts for upstream research would almost certainly foster a needless barrier to both science and global public health, one that scientists will resist, disregarding any difficulties of implementation and enforcement.

As matters stand, any researcher wishing to publish internationally must lodge data with the open-access system, including researchers from biodiversity-rich countries working on domestic species (Rohden and Scholz, 2021). However, if governments restrict this practice over time, it will become hard for local researchers to collaborate and publish internationally. Ironically, if publication or GSD use becomes restricted by governments, or if the industry cannot acquire legal certainty to use these resources, research may shift (and already has in some cases) to countries that do not have ABS measures or to nonparties to the Nagoya Protocol. This can not only limit the understanding of Earth's biodiversity but also bias global scientific and public health research and development, such as in the case of the annual development of globally comprehensive seasonal influenza vaccines.[20]

Although many scientific journals still impose restricted (paid) access on their publications, after the genomic revolution – with the Human Genome Project and the adoption of the Bermuda Principles (Collins et al., 2003)[21] – there has been a strong trend toward the Open Science movement, with free sharing of GSD and

[20] WHO (2016) noted that the Nagoya Protocol has challenged the development of comprehensive and effective seasonal influenza vaccines, with the difficulty of including influenza strains from countries that have in place strict ABS regulations and time-consuming compliance processes.

[21] The Bermuda Principles set out rules for the rapid and public release of GSD. The Human Genome Project, a multinational effort to sequence the human genome, generated vast quantities of data, but even more remarkable than that was the speed at which that data has been released to the public, under the umbrella of the Bermuda Principles.

related scientific data. Restricting this previously achieved freedom in data access, use, and sharing would constitute a regrettable step backward.

13.4 OTHER FACTORS BEARING ON COLLABORATIVE RESEARCH UNDER THE CBD

Assuming that the prior proposal merits serious attention, there is a further need to consider how existing policies governing the production, storage, and distribution of pathogens and related GSD would need to be adapted in conformity with such a global multilateral arrangement. In what follows, the authors describe some current and innovative practices already being adopted for the management of both genetic resources and GSD. Also assessed are some remaining challenges to conforming the sharing of pathogen GSD to the overall ABS infrastructure.

13.4.1 *The Key Role of Open and Semi-Open Repositories for GSD*

The use of sequencing technologies revolutionized the scientific community's understanding and management of plant, animal, environmental, and human health. However, their optimal use has been dependent on the willingness and ability of countries to share relevant GSD. In this context, GSD function as inputs and outputs of the research process that should be made widely available for further research and public health purposes. This dual functionality has, in turn, elicited growing demands to place GSD in public repositories (WHO, 2017). Such repositories can be open to all legitimate users in the form of what is often labeled as a "commons" (Ostrom, 1990). In appropriate cases, access and use may be limited to specified communities that have collectively contributed to and managed the repositories in question, as would occur under a "semi-commons" (Reichman et al., 2015).

The most prominent open-access approach to sharing pathogen GSD is the INSDC in which 95 percent (705 out of 743 at the time of writing) of all relevant databases directly link to or download their sequence data (Rohden and Scholz, 2021).[22] The INSDC has adopted a policy that rejects conditions that impose any restrictions on accessing its stored data, thereby enabling every person and institution, regardless of their background and intended use, to access these resources (Brunak et al., 2002). This data-access model is the most prominent example of an existing repository completely compatible with the Open Science movement. At this time, however, its very openness also poses the biggest challenges for monitoring ABS compliance. Efforts to make the INSDC open-access policies consistent with

[22] This analysis was based on more than 1,600 biological databases listed in the annual publication of the *Nucleic Acids Research Database Issue*, which promotes understanding of the GSD database landscape and structure.

the multilateral approach proposed in this chapter could facilitate ABS implementation for pathogen resources generally. This follows because the GSD could be freely shared for noncommercial uses in keeping with the recognition of the nonmonetary benefits of Open Science. By the same token, a "change of intent" clause with regard to monetary benefit sharing could later be imposed through binding SMTAs as needed.

In contrast, a good example of a semi-commons model for sharing pathogen GSD was established by the Global Initiative on Sharing All Influenza Data (GISAID EpiFlu) (n.d.) as the global database for sharing influenza gene sequences and related metadata. GISAID plays an essential role in sharing influenza sequences among the WHO Collaborating Centers and National Influenza Centers under the WHO's Pandemic Influenza Preparedness Framework for biannual influenza vaccine virus recommendations (WHO, 2014). The GISAID (2011) data-access policy is based on a legally binding agreement that every user must sign before being granted access. Users are not allowed to share GISAID's sequence data with other nonsignatories to the agreement. GISAID thus provides an alternative to public domain databases in which data providers and users are not identified. Through its access agreement, GISAID could likewise provide a basis for monitoring and enforcing compliance with ABS obligations under the CBD. The GISAID model also addresses some of the inequality issues in open-access systems through the binding conditions in its data-access agreement, which stipulate that users acknowledge data providers in future publications and, when possible, engage them in research efforts.

Another recent initiative of interest was the Collaborative Management Platform for Detection and Analyses of (Re-)Emerging, and Foodborne Outbreaks in Europe (COMPARE) (2015), a major European Commission research project to which some of the authors of this chapter were external advisors and others were Consortium members. This project addressed the need to make sequence data broadly available to support rapid containment, identification, and mitigation of emerging infectious diseases and foodborne outbreaks. To accomplish this goal, COMPARE developed a database and sharing platform for GSD from diverse pathogens, enabling stakeholders in the human health, animal health, and food safety domains to readily access and use these same resources under a One Health approach (Gibbs, 2014).[23] To address inequalities in bioinformatics and data-analytics capacity, COMPARE (2015) also offered free online analytical tools that could help scientists and other users from ill-equipped institutions and countries to analyze and interpret the available data without having to mobilize large amounts of resources in computer memory and data storage.

Within its broad investigation of barriers to data sharing, the COMPARE project identified specific stakeholder groups with different interests to be taken into

[23] The One Health approach is defined as the collaboration of professionals from different fields to support human health, animal health, and environmental resilience.

account when devising their roles as potential users of the COMPARE platform (Ribeiro et al., 2018b). The project nonetheless recognized that even these legitimate concerns should not block the timely and open sharing of data, which would compromise the project's primary objectives. In addressing this quandary, COMPARE established separate data hubs in which sensitive data could be shared only among an agreed group of stakeholders under confidentiality terms, on the condition that after a reasonable period (six to twelve months, in general), that same data could ultimately be placed in the public domain. By means of this temporary embargo, which could be deemed a semi-commons arrangement, a delay in public sharing became acceptable when necessary. This model also addressed other key barriers to data sharing, including the need to allow a priority of use for analyzing the data by local researchers in provider countries while also enabling long-term access and use of the same data for legal research purposes. The model thus established a trusted environment for the prepublication of data with relevant stakeholders who might otherwise have been reluctant to deposit the data directly in the open-access site.

13.4.2 *Further Policy Considerations*

Looking beyond the question of access to pathogen GSD via either public or more restricted repositories, the sharing process under the CBD still requires attention to other important policy issues. First, the nature of the benefits at stake has evolved, with research collaborations, capacity building, and technology transfer modalities taking on new forms through the sharing of software, analytical tools, and other technologies, as well as increased sharing of GSD (and components thereof). As previously discussed, promising new research arrangements in the form of "global commons" or "semi-commons" (Reichman and Okediji, 2012, Reichman et al., 2015) both retain attribution and coauthorship as benefits and, in some cases, authorize more complex research collaborations in lieu of monetary rewards. These approaches are especially useful in precompetitive phases, when commercial applications for the resources or knowledge at issue are not yet, or may never be, established.

In addition, distinctions between "commercial" and "noncommercial" research should yield different implications for benefit sharing under the CBD. Yet, the lines between these two categories have become blurred in recent decades, as academic and government researchers increasingly partner with industry or otherwise act commercially (Overmann and Scholz, 2017), and as the industry itself also contributes noncommercial findings and research to upstream research projects. In the public health field, this distinction becomes even more complex, given that the development of pharmaceutical products to respond to epidemics and other disease outbreaks sometimes generate low-profit margins (if any) and are increasingly subsidized by governments and health agencies in public–private partnerships (Van de Burgwal et al., 2018).

Although a multilateral system could authorize noncommercial research under SMTAs, while a "change of intent" clause would still cover subsequent decisions to use research results in commercial applications (art. 8(a) of the Nagoya Protocol), the practical distinctions concerning when and in which specific cases commercial use is to be triggered would need to be defined. In practice, the authors acknowledge that there are limits to the technical legal device of "change of intent" clauses, especially in cases where GSD are shared in the public domain. Because such sequences move fluidly between commercial and noncommercial institutions, once uploaded to open-access databases, they become available for all to use, regardless of the distinction between the two types of use.

Tracking and tracing GSD to monitor their access, use, and sharing are also essential steps to the enforcement of ABS compliance and, at the same time, constitute a major challenge for the inclusion of GSD within the scope of the Nagoya Protocol. From a purely technical perspective, these issues depend on the implementation of technologies that enable the tracking, tracing, and monitoring of genetic resources (Rohden and Scholz, 2021). But even when tracking becomes technically more reliable, it may not fully resolve some managerial problems. For example, with or without tracking, questions could remain as to who did the work that led to commercialization; what GSD they employed; who the owners of the sequences in question are; and what rights they should have, if any, against those who solved the problem that produced a commercial application (Butler, 2013).[24] Moreover, monetary benefits flowing from the use of GSD remain inherently speculative due to challenges in identifying both the provenance and value of any given sequence or its components in complex applications.

Another fundamental issue to be addressed under a multilateral framework is ensuring that benefits are shared with legitimate providers and that they otherwise contribute to the original objectives of the CBD and its Nagoya Protocol. Grantors that fund research projects likely to involve pathogens and other related sequence data should expressly require grantees to comply with the CBD and Nagoya Protocol and, in particular, their ABS obligations. This approach would thus resemble the typical requirements of grantees to respect intellectual property rights under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement). In appropriate cases, funders could also require that GSD resulting from a grantee's project be deposited in designated and certified repositories.

[24] In the case of MERS, there were endless discussions on the patenting of the virus coming from a Saudi patient by a Dutch lab. Under strong criticism from the international community (in the 2012 World Health Assembly), the Dutch scientists claimed that the reason for patenting the virus was to be able to rapidly develop diagnostic tests and make them available to affected countries, which could be a different situation if a commercial company had owned the patent.

CONCLUDING OBSERVATIONS

A primary goal in writing this chapter was to help avoid the risk that intellectual property treaties and related administrative initiatives might disrupt the use of pathogens for public health research purposes. Consistent with the CBD and the Nagoya Protocol's legal framework, we propose a narrow but workable approach that aims to remove the "coverage" issue as the focus of attention from discussions of the COP, specifically concerning pathogen material and including GSD, however ultimately defined. Under this approach, those who legally access pathogen resources covered in an MoU should officially be granted a legal right of use under the CBD for noncommercial purposes in lieu of bilateral access and benefit-sharing agreements.

All such uses would, however, become subject to a built-in "change of intent" clause recognizing the respective users' liability for specified benefit-sharing royalties from any eventual commercial applications of the initially exempted materials or data. The codified multilateral solution for pathogens in this chapter could alleviate the need for agreement on more complex issues. It could also provide a flexible means of facilitating scientific research on pathogen GSD without compromising the interests of diverse stakeholders under the CBD while rebuilding trust among the parties.

The history of the Nagoya Protocol is marked by polarization between provider and user countries (Muzaka and Serrano, 2020). Because these groups perceive their interests as conflicting, they tend to focus their arguments on the protection of national interests rather than on the achievement of a common goal. Discussions concerning proper access to and use of genetic resources were already somewhat compromised by the adoption of the TRIPS Agreement in 1994, when international intellectual property law began to limit access to and the availability of such resources generally, with a resulting deficit in trust (Reichman, 2018; Six et al., 2015). From this perspective, the CBD itself may be perceived as a developing-country response to the TRIPS Agreement negotiations, one that protects inputs to innovations from developing countries and not just outputs from developed countries (Dreyfuss and Ng, 2018).

Meanwhile, the variety of stakeholders involved in managing genetic resources, with their diverse and often conflicting interests, tends to engender growing mistrust. The politicized nature of the decision-making environment within the CBD may sometimes prevent stakeholders from fully evaluating the practical implications of the enforcement measures embodied in the Nagoya Protocol. It also seems advisable that contributors to scientific research and public health should be better represented within the governing apparatus of the CBD itself.

To rebuild trust in the process of sharing genetic resources, including GSD, the concerns of all stakeholders should be taken into consideration and translated into common goals. To this end, realistic expectations must be built into an improved governance system that will not hamper the freedom to access, use, and share essential inputs for research and public health that generate societal benefits. The objective should be to support fair and equitable collaborations and the sharing of

benefits in innovative ways that conform to the needs of technological and infrastructural developments and resulting applications.

Instead of expecting stakeholders to surrender secrecy, control, and exclusivity due to extrinsic monetary incentives, a trustworthy system of collective action should focus on alternative values rendering the discussion more practical and fruitful. These additional values would reflect both common informal norms and codes of conduct arising from the exploration of biodiversity and from scientific and public health practices that embrace principles of reciprocity, openness, and collaboration (Six et al., 2015).

As discussed throughout this chapter, inequalities exist in terms of public health capacity, bioinformatics, and data-analytics capacity. A bilateral ABS mechanism, however, is unlikely to address these inequalities, as there are no guarantees that the funds will be invested in capacity-building initiatives. The countries with more data collection and sequencing capacity will share more GSD and therefore receive most of the benefits, reinforcing the existing gaps. In a truly multilateral system, benefit-sharing funds can instead be invested in countries with the biggest needs – for example, in data-analytics capacity building or epidemic response during a public health crisis. This represents a more sustainable approach to ABS when, in the future, developing countries can more equally profit from open science and open-data structures and policies.

A number of collective networks and sharing platforms are already experimenting with innovative governance arrangements, and their lessons and experiences should constitute valuable inputs for future CBD discussions. Any proposal for a feasible and sustainable solution should move away from burdensome, costly, and time-consuming bilateral negotiations to ensure globally harmonized governance rules covering the rights and obligations of all the parties that are unambiguous and universally applicable.

The ultimate goal should be to ensure that research on pathogens proceeds under fair precepts of global cooperation while enforcing ABS obligations under the CBD in the least intrusive manner possible. The proposals set out in this chapter strive to promote these objectives. The authors thus urge the COP to simplify their negotiations in this respect, with a view to better promoting both science and the larger social welfare interests at stake while updating the objectives of the CBD to better reflect the evolution of scientific research methods, technological developments, and global health over time.

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