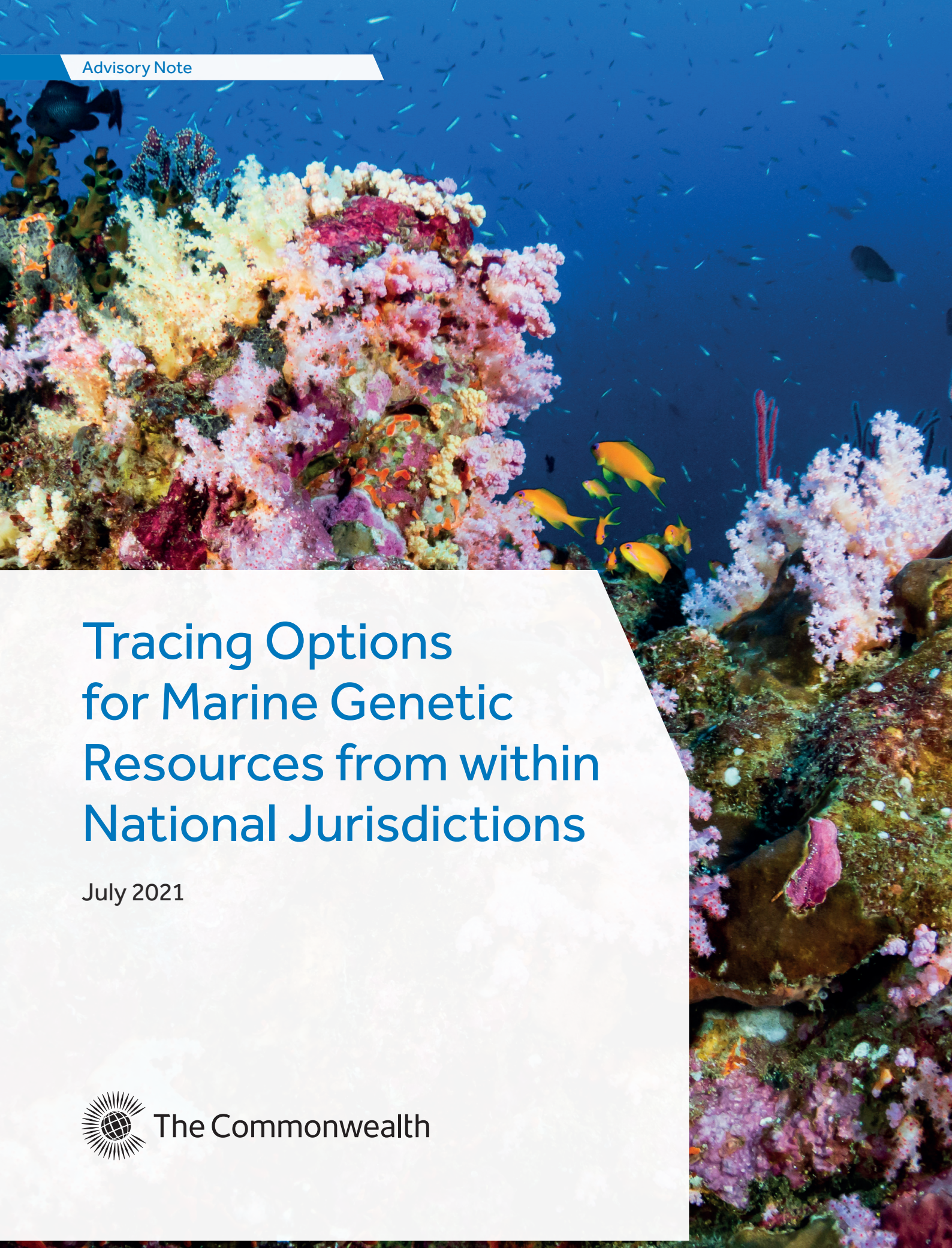
Advisory Note



Tracing Options for Marine Genetic Resources from within National Jurisdictions

July 2021

The Commonwealth

ADVISORY NOTE

Tracing Options for Marine Genetic Resources from within National Jurisdictions

London, Marlborough House

July 2021

The Commonwealth
Blue Charter

Report prepared by

Marcel Jaspars
Marine Biodiscovery Centre, Department of Chemistry,
University of Aberdeen, UK

Fran Humphries
School of Law, Queensland University
of Technology, Australia

Muriel Rabone
Deep-Sea Ecology and Systematics
Group, Life Sciences Department, Natural
History Museum, London, UK

Reviewed by

Alison Swaddling
Oceans and Natural Resources,
Commonwealth Secretariat

Jeff Ardron
Oceans and Natural Resources,
Commonwealth Secretariat

Published by the Commonwealth Secretariat.

Contents

Abbreviations and Acronyms

ABS	Access and Benefit-Sharing
ABSCH	Access and Benefit-Sharing Clearing House (the CBD clearing house mechanism)
AN	Accession Number (specifically for INSDC database entries; these represent a unique identifier for a record within the INSDC system)
BBNJ	The proposed legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity in areas beyond national jurisdiction
CBD	Convention on Biological Diversity
CAN	Competent National Authority
DOI	Digital Object Identifier
DSI	Digital Sequence Information
eDNA	environmental DNA
EU	European Union
FAIR	Findable, Accessible, Interoperable and Reusable
GBIF	Global Biodiversity Information Facility
GEF	Global Environment Facility
GGBN	Global Genome Biodiversity Network
GUID	Globally Unique Identifier
INSDC	International Nucleotide Sequence Database Collaboration
IP	Intellectual Property
IRCC	Internationally Recognised Certificates of Compliance
IT	Information Technology
ITPGRFA	International Treaty on Plant Genetic Resources for Food and Agriculture
MAT	Mutually Agreed Terms
MGR	Marine Genetic Resources
MTA	Material Transfer Agreement
NCI	National Cancer Institute
OBIS	Ocean Biodiversity Information System

PIC	Prior Informed Consent (also known as Free, Prior and Informed Consent – FPIC – in agreements outside of the Nagoya Protocol.)
PNPRC	Pacific Natural Products Research Centre
SMEs	Small and Medium Enterprises
SMTA	Standard Material Transfer Agreement
UID	ABSCH Unique Identifier
UNDP	United Nations Development Programme
US	United States
USP	University of the South Pacific
WiLDSI	Scientific Approaches for Digital Sequence Information
WIPO	World Intellectual Property Organization
WoRMS	World Register of Marine Species

List of other key terms

ABSCH unique identifier: The identifier allocated by the ABSCH, unique within that system

Assay: Tests undertaken to indicate bioactivity against diseases

Bioactivity: Biologically active level of the given substance/ compound, often at a certain level against a human disease model

Bulk identifier: A collection level or bulk specimen lot identifier (see "specimen lot")

Derivative: "Naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity" (Article 2 Nagoya Protocol)

Extract: A complex mixture of small molecules obtained from an organism or microbial fermentation using chemical solvents

Sampling event: The collection or sampling at a given locality and timepoint (e.g. a box core sample recovered from the sea floor or a trawl recovered from the water column would be considered a discrete sampling event)

Specimen lot: Mixed unsorted sample, generally containing different species but from one sampling event, for example where all the organisms from a trawl are preserved and stored in one container for future identification/analysis

Executive Summary

Introduction: Some marine organisms may contain substances with potential applications, for example in pharmaceuticals, personal care products, nutraceuticals, agriculture, aquaculture, biofuels and biotechnology. Tracing eventual products back to the marine organism from which they were initially derived can be challenging as it entails looking at the various phases, including the scientific research, development and eventual commercialisation phases. Traceability is nevertheless necessary to provide evidence as to whether a share of the benefits is owed to the provider of the resource. It is a complex and multidisciplinary process, involving legal, scientific and database/informatics considerations. This report looks at the scientific background to traceability and how different approaches to traceability may work in practice. Two case studies accompany this report, to show how current Access and Benefit-Sharing (ABS) and traceability processes work in Fiji and South Africa, both of them parties to the Nagoya Protocol.

The Nagoya Protocol: ABS is a legal framework under the Convention on Biological Diversity (CBD) that requires States Parties to aim to facilitate access to genetic resources within their jurisdiction and to take legislative, administrative or policy measures to share the results of research and development on the benefits of commercial and other uses of genetic resources in a fair and equitable way. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the CBD implements the ABS concept. Discussions are ongoing regarding whether genetic resources-associated information/ data (Digital Sequence Information – DSI) should be included as part of the ABS transaction, and, if so, how to achieve this in practice.

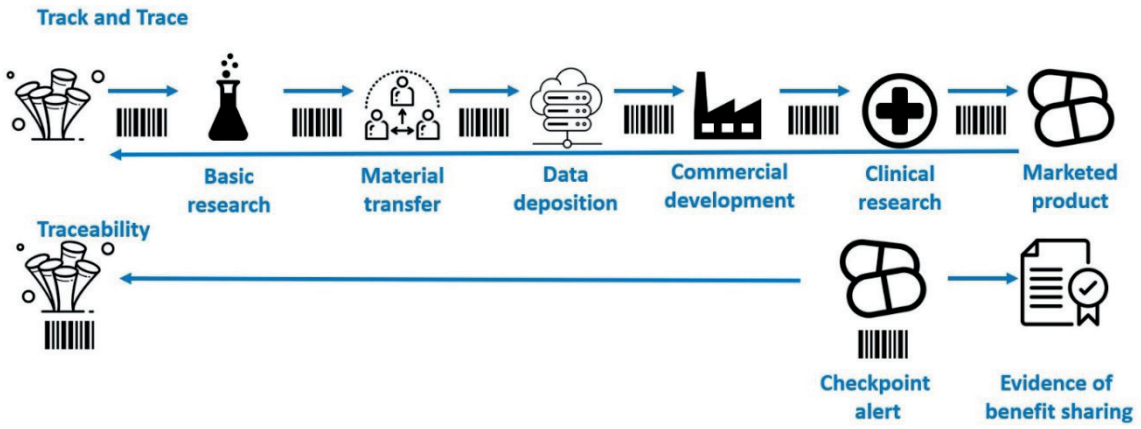
Marine bioprospecting: Almost 65 per cent of all pharmaceuticals have their origin in nature, although many have been modified heavily from the substance found in the original organism. Success rates have been found to be particularly high for soft-bodied marine invertebrate-derived substances compared with those obtained from terrestrial organisms. Globally, however, marine bioprospecting, mainly on reef-dwelling invertebrates, has yielded only 15 clinically used pharmaceuticals to treat cancer, pain, viral infections, and heart disease over the past 70 years. The process of drug discovery is lengthy, complex and resource-intensive. A great number of small molecules (~2,500) enter the pipeline for every successful drug that is approved and marketed.

Given the funds required for drug development and the complexity involved in running clinical trials, most of this is done by industry. Commercial users commonly limit the visibility and sharing of commercially valuable materials and information so as to protect their investment. This may mean that it is harder to trace materials and associated information through the commercialisation phase. The dominant model for marine bioprospecting globally is one that starts with academic research to yield candidate compounds for preclinical evaluation, which may be licensed to large pharmaceutical companies or form the basis of university spinout companies.

Many different types of benefits, both monetary and non-monetary, may result for the country of origin from the use of their marine genetic resources (MGR). Monetary benefits may be based on royalty payments, milestone payments or occasionally upfront payments for access to materials. Non-monetary benefits are often described in terms of capacity-building, such as through the training of scientists; research collaborations, including the co-authorship of publications and joint grant applications; and the building of scientific infrastructure.

The starting point for bioprospecting is sample collection – whether through marine scientific research activities or, less commonly, through collections specifically for bioprospecting purposes. These sampling events are allocated a code or identifier; after samples have been sorted, they are allocated an in-house identifier as well. A unique or persistent identifier is allocated when material is deposited in the collections of a research institution or company. During subsequent laboratory work, the specimens may be further analysed. As part of the process, subsampling often occurs, and this may result in the generation of a large number of subsamples. Specimen data is often shared globally via the Global Genome

Figure E1. Comparing track and trace and traceability approaches



Note: The steps in the track and trace approach exemplify the types of processes involved in product development. Unique identifiers are indicated using bar codes. Graphics are from the Noun Project.

Biodiversity Network, and DNA sequences are stored in the International Nucleotide Sequence Database Collaboration (INSDC) databases. Usage of identifiers in databases and publications is key to the traceability of MGR samples/collections and data during the research phase of bioprospecting.

Once marine specimens have been obtained, the process of discovering potential commercial value can start – a process often involving several steps using chemical and biological expertise. The end result is the discovery of a purified compound with biological activity against disease. Tracing the often hundreds or thousands of samples and subsamples through this process is challenging but can be achieved using good laboratory practice often involving in-house databases.

Traceability policy options and implications: Governments may have ABS infrastructure and identifiers, assigned for reasons related to traceability in the administrative or legal sense. Whereas scientific identifiers associated with a record are generally globally unique and persistent, allow for the linkage of information between databases (including across jurisdictions) and are relatively easy to retrieve, legal or administrative mechanisms and associated identifiers rarely share these attributes. The Nagoya Protocol has frameworks for both ABS measures and monitoring and compliance measures. Within this, it covers Prior Informed Consent (PIC) from the provider of the genetic resource and traditional knowledge associated with it, as well as sharing in the benefits of its use on Mutually Agreed Terms (MAT). The Protocol also requires States Parties to take measures to monitor and enhance transparency on the utilisation of genetic resources, including through a system of checkpoints and Internationally Recognised Certificates of Compliance. The Nagoya Protocol model only tracks PIC and MAT obtained under the national law of the provider country, and not whether users have complied with the terms of a benefit-sharing agreement or whether subsequent users of the genetic resources are similarly bound to benefit-sharing. The main challenge to this system therefore lies in tracing the movement of genetic resources across borders and how to address instances of non-compliance.

Tracing material can be achieved either via a full track and trace system, which has a very high administrative burden, or via a lighter-touch traceability system (Figure E1), with various options between. It should be noted that, under the Nagoya Protocol, track and trace is not an explicit element of traceability. Table E1 summarises several different systems, showing how these place the burden of compliance on the initial researcher or end user.

Conclusions: There need not be a one-size-fits-all approach to traceability mechanisms. Diverse approaches, developed to suit local research and development environments, can achieve similar traceability outcomes. Consideration needs to be given in each country to the potential impact of systems developed with regard to basic research, their practicality in terms of achieving traceability objectives and their resourcing implications.

Table E1. Summary of the opportunities and challenges of the different traceability systems

Traceability system	Opportunities	Challenges
Track and trace Location of all samples known. Every movement of sample recorded. Direct link between end user and provider.	Could use national measures developed for Nagoya Protocol: reporting requirements, identifiers, checkpoints, change of use, third-party transfer provisions.	Tracking samples across borders. Gaps in Nagoya Protocol monitoring mechanisms. Compliance burden placed on initial researchers not end users. Systems likely to be high cost.
Contractual/licensing Benefit-sharing negotiated directly between provider and user.	Standard Material Transfer Agreements (SMTAs) reduce compliance burden by providing standard terms and conditions. SMTAs can be made machine-readable, aiding traceability. Machine-readable creative commons licences could be used for DSI.	Countries have not agreed on standard conditions under a multilateral system that are consistent across countries. Third-party transfer often precluded, increasing burden on researchers to negotiate this on a case-by-case basis.
End user Downstream users report on **activities** at which point certain obligations, such as reporting, disclosure or benefit-sharing obligations, are triggered.	Low impact on research: obligations for reporting and benefit-sharing are triggered only once economic exploitation arises linking end user to provider.	Resources and infrastructure (including checkpoints and databases) are still required to link the end use product or activity back to the original sample/information.
End product Downstream users report on **products** at which point certain obligations, such as reporting, disclosure or benefit-sharing obligations, are triggered	Low impact on research: disclosure of origin combined with other traceability mechanisms, including unique identifiers and patent office checkpoints, could support traceability across jurisdictions.	Patented discoveries may be further developed making original MGR hard to trace. Different intellectual property systems in different jurisdictions may leave traceability gaps. Some products are not patented.
Open Access Open Access databases and repositories may be used to trace the movement of both data and physical samples.	Builds on good scientific practice and existing databases/ repositories. Research norms encourage compliance.	Not all collections are globally discoverable or accessible. Better linkages between databases required. Relies on databases and repositories receiving long-term funding.
Combined approaches Elements of the above strategies may be combined. Traceability approaches may be tailored to the type of resource or activity being carried out with it.	Builds on good scientific practice. A series of possible options would be available to subsequent users of the MGR or data derived from them.	Would need to be developed with a clear traceability strategy. Might import challenges identified in the options above if those options are included in the combined system.

No solutions exist for traceability that meet all requirements discussed in this report. Full track and trace is complex, requiring substantial systems development and maintenance; is very resource-intensive; and requires co-ordination across different disciplines, from marine scientific research and informatics to law and policy. A bespoke track and trace system would be costly and take years to develop, and may face resistance and limited uptake from users. It would also require co-operation across multiple jurisdictions.

Future financial gains from bioprospecting are very uncertain and may not cover the costs associated with a full track and trace system.

Approaches likely to be successful should build on existing global infrastructure, use procedures developed in other policy instruments or be a combination of approaches in Table E1. There are existing scientific networks that can support traceability, particularly in terms of databases such as the INSDC for DSI and the Ocean Biodiversity Information System (OBIS) for species information. Efforts to co-ordinate bioprospecting on MGR in a region should be encouraged, as should initiatives that make MGR data available openly, as this will advance scientific development and understanding of marine biodiversity.

1. Introduction

Some marine organisms may contain substances with potential applications, for example in pharmaceuticals, personal care products, nutraceuticals and biotechnology. In a few cases, the marine organisms are harvested to generate the final commercial product, but generally it is the information obtained from these organisms that is utilised to create the product. Tracing eventual products back to the marine organism from which they were initially derived can be challenging as it entails looking at the various phases, including the scientific research, development and eventual commercialisation phases. Traceability is nevertheless necessary to provide evidence as to whether a share of the benefits is owed to the provider of the resources. It is complex and multidisciplinary, involving legal, scientific and database/informatics considerations.

This report looks at different aspects of traceability, including the scientific background to bioprospecting, the implementation of traceability in marine scientific research and how different current and proposed traceability systems may work, including their advantages and disadvantages. The report ends by providing policy considerations and some overall conclusions.

Two case studies accompany this report, showing how current Access and Benefit-Sharing (ABS) and traceability processes work in two different parties to the Nagoya Protocol. The first study is of Fiji, a small island developing state, where a great deal of international collaborative marine bioprospecting has been carried out over the past 50 years. The Fijian system relies on the excellent relationships built up over long periods between Fijian researchers and their international collaborators and is an example of a "light-touch" system. The second case study discusses South Africa's more formalised and regulated system for ABS and traceability. Section 4 of the report discusses the relative benefits and disadvantages of each approach.

1.1 The Nagoya Protocol on Access and Benefit-Sharing

ABS is a legal framework under the Convention on Biological Diversity (CBD) that requires States Parties to aim to facilitate access to genetic resources within their jurisdiction and to take legislative, administrative or policy measures to share the results of research and development on the benefits of commercial and other uses of genetic resources in a fair and equitable way (CBD Article 15). The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the CBD implements the ABS concept. This includes a framework on Prior Informed Consent (PIC) from the provider of the genetic resource and traditional knowledge associated with it, as well as on sharing the benefits of its use on Mutually Agreed Terms (MAT). The Nagoya Protocol also requires States Parties to take measures to monitor and enhance transparency on the utilisation of genetic resources, including through a system of checkpoints and Internationally Recognised Certificates of Compliance (IRCC).

The CBD defines "genetic resource/resources" as follows: "'Genetic material' refers to any material of plant, animal, microbial or other origin containing functional units of heredity. 'Genetic resources' refer to genetic material of actual or potential value" (Article 2). Additionally, the Nagoya Protocol defines the term "derivative": "'Derivative' means a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity" (Article 2). It clarifies that ABS relates to the "utilization of Genetic Resources," which means "to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology" (Article 2). In other words, unless national measures state otherwise, ABS generally relates to the genetic materials and derivatives used in the course of research, development and/or commercialisation for their genetic properties and not for other attributes (such as the trade in bulk commodities or biotrade).

Table 1. Key differences between samples and data relevant to traceability of marine genetic resources

Information/data	Specimens/samples
Using information does not stop anyone else from using the same information	Specimens/samples are limited in quantity/ finite by nature and can potentially be used up
Once the first copy of the information is made, the cost of making additional copies is marginal	Obtaining additional material may be expensive and obtaining "identical" samples is not possible
Once information is known, it is hard to exclude others from using it in practice	If materials are not discoverable or are bound by legal/contractual agreements, they may not be accessible

Discussions are ongoing at the Conference of the Parties to the CBD and other forums relating to ABS frameworks[1] regarding whether a genetic resources' associated information/data (known as Digital Sequence Information – DSI) should be included as part of the ABS transaction, and, if so, how to achieve this in practice.[2] DSI is a placeholder term and there is no agreement among countries as to what is meant by it, although attempts are being made to clarify it.[3] Regardless of what is debated at the international level, though, there is wide variation in terms of the materials, derivatives, information, knowledge and activities that countries include in the scope of their national ABS measures (Humphries et al., 2021a). This means the subject matter that falls within the scope of traceability requirements needs to be assessed on a country-by-country basis.

This report uses the term marine genetic resources (MGR) as a subset of genetic resources (referencing both the physical specimen and the associated data – DSI). MGR does not have a specific meaning under international regimes,[4] and the report uses the term to mean genetic resources from marine environments that fall within a country's definition of genetic resources (physical specimens/samples and/or derivatives).[5] Derivatives are important for questions of traceability as it is often these substances that are commercialised, for instance proteins or small molecules with useful functions. It is worth noting here that physical specimens and DSI are interlinked but distinct entities. Table 1 summarises key differences relevant to MGR and associated data. This report outlines how DSI might be tracked alongside the associated MGR, and consequences for traceability.

1.2 The marine bioprospecting landscape

Almost 65 per cent of all pharmaceuticals have their origin in Nature, although many have been modified heavily from the substance found in the original organism ("derivative" as defined in Section 1.1; Newman and Cragg, 2020). The percentage of compounds from soft-bodied marine invertebrates that show potent and selective biological activity against human disease targets is far higher than for compounds obtained from terrestrial organisms (The Royal Society, 2017). This may be because such invertebrates have no obvious protection and may use chemical defences instead. Additionally, as some marine invertebrate groups (e.g. sea cucumbers) have known tissue regeneration abilities, they present a natural starting point for the investigation of medical/cosmetic applications. Globally, marine bioprospecting over the past 70 years has yielded only 15 clinically used pharmaceuticals to treat cancer, pain, viral infections and heart disease.[6] Most of these pharmaceuticals have been discovered through research on reef organisms such as ascidians (seasquirts), sponges and cyanobacteria, excepting the heart medications, which have been obtained from oily fish. Most were discovered and developed before the CBD was ratified in 1993 and well before the Nagoya Protocol came into force in 2014, and therefore it is not clear whether benefits were shared with the source countries.

The process of drug discovery is lengthy, complex and resource-intensive (Simpkin et al., 2017). A great number of small molecules enter the pipeline for every successful drug that is approved and can be marketed (Figure 1 presents indicative timelines, success rates and costs for each stage). Several phases of clinical trials must be completed before a pharmaceutical can be approved; if

preclinical animal trials show positive data, a decision may be made to start human clinical trials, which requires a scale-up of production of the compound and multi-million dollar budgets to run such trials in multiple locations. Success rates can be low from Phase I through to Phase III clinical trials, and, even if successful, the compound may not receive regulatory approval.

Given the funds required for drug development and the complexity involved running clinical trials, most of this is done by industry. Commercial users commonly limit the visibility and sharing of commercially valuable materials and information to protect their investment. This may mean that it is harder to trace materials and associated information through the commercialisation phase. For clinical studies, trial design and data should be made available publicly.[7] An added complexity is that compounds that enter clinical trial may be unrecognisable compared with the compounds initially discovered, making accurate tracing even more complex. To confound matters further, the same compound may have several names – a common name and associated chemical name, the name used during clinical trials and a separate name for the marketed pharmaceutical.

Figure 1 shows representative timelines, the attrition of compounds from the start to end of the bioprospecting process, the different clinical trial phases from preclinical to approval, representative costs and success rates of clinical trials. Different phases of the process are carried out by different actors (universities, small and medium enterprises (SMEs), large pharmaceutical companies) and cover phases that range from basic research, which generates scientific knowledge and data, to eventual commercialisation. Potential and actual value are also indicated.

Since the number of compounds from MGR that enter clinical trials is limited, they are often tracked by specialist websites such as Marine Pharmacology,[8] which ensure current data is available on the progress of such compounds through industry-sponsored trials. Besides listing the marine-derived pharmaceuticals that have been approved, this website shows that currently five are in Phase III, 12 are in Phase II and 16 are in Phase I, with several hundred candidates under preclinical evaluation. Given that nearly 37,000 compounds have been discovered from marine sources[9] and only 15 have been marketed as pharmaceuticals, this gives a success rate of one pharmaceutical agent discovered for every 2,500 compounds discovered which compares favourably to terrestrial sources. Box 1 summarises challenges associated with the discovery of pharmaceuticals from marine organisms.

The dominant model for marine bioprospecting globally is one that starts with academic research to yield candidate compounds for preclinical evaluation, which may be licensed to large pharmaceutical companies or may form the basis of university spinout companies, such as Nautilus Biosciences Canada Inc.,[10] which aims to discover agents for human and animal health from marine-derived microorganisms. Industry, typically university spinouts and SMEs, may be involved in marine bioprospecting from the outset; successful SMEs include PharmaMar SA of Spain,[11] which has marketed several successful pharmaceuticals. Although its first marketed anti-cancer agent, Yondelis, was developed based on an academic discovery (see Annex 1 for an overview), the company has also been involved in bioprospecting expeditions globally to discover further potential pharmaceuticals. Most big pharmaceutical companies no longer invest in bioprospecting directly, but may collaborate with academic institutions. An example was the 15-year relationship between Griffith University and AstraZeneca (now ended) to explore Australian terrestrial and marine biodiversity. The academic part of this collaboration continues as NatureBank,[12] which allows access to external researchers under an MTA.

1.3 Potential benefits from the use of marine genetic resources.

Many different types of benefits, both monetary and non-monetary, may result for the country of origin from the use of MGR. Monetary benefits may be based on royalty payments, milestone payments or occasionally upfront payments for access to materials. As an example, the anti-cancer agent Halaven (Annex 1) had annual sales of around £250 million in 2017. Determination of royalty payments is usually through negotiation between provider and user. Some countries have set a level (e.g. Brazil at 1 per cent of annual net revenue), but even this may be negotiable. One of the problems inherent in ABS lies in inflated expectations regarding potential

royalties, and there is very little understanding or analysis of the meaning of "fair and equitable" under the Nagoya Protocol (Tiller et al., 2020).

Non-monetary benefits are often described in terms of capacity-building, such as through the training of scientists; research collaborations, including co-authorship of publications and joint grant applications; and the building of scientific infrastructure.[13] Given that "non-monetary benefits" for the most part require significant resources, the term can cause confusion and it may be better to delineate different types of benefit-sharing based on when and where they occur in the marine scientific research, bioprospecting research or development process. Capacity-building efforts, for example, occur at the start of the process, whereas monetary benefits may not transpire until the product is commercialised and profitable, which may take decades (Figure 1, Box 1).

Box 1. Challenges associated with the discovery of pharmaceuticals from marine genetic resources

Marine bioprospecting typically starts with the collection of a marine organism, followed by chemical extraction and testing of the extract in a disease-focused screen (Figures 2 and 3). Biologically active compounds are isolated and structures characterised; this is followed by preclinical evaluation in animals. If the situation is promising at this stage, the main challenge lies in obtaining sufficient material for clinical trials. Annex 1 describes these for the discovery of two marine pharmaceuticals from marine invertebrates. From these two examples, the following challenges are evident:

- The process is lengthy, taking a period of decades from initial identification of biological activity until a product is approved for clinical use and can be marketed to generate a profit.
- Organisms containing the compound of interest are not always unique to one location – they may occur in multiple jurisdictions. Multiple researchers may discover the same compound.
- The process is non-linear and often discontinuous, with many starts and stops along the way and multiple actors taking part in the discovery.
- Initial research is fundamental in nature – for example taxonomy/biodiversity research and associated ecological studies. It generally takes place in public research bodies (universities/research institutes/museums), publicly funded by national funding agencies and charities.
- Industry may be involved from the start of the research or (more commonly) may become involved when a compound of interest is identified. Industry partners may change throughout the development process.
- Clinically approved materials are rarely obtained from wild collections, and are mainly produced via chemical synthesis, semi-synthesis or biotechnological processes. In many cases, analogues are developed and marketed, not the original chemical structure.
- Multiple patent families exist for each product, starting with the original chemical structure and material followed by the means of production of the finally approved compound.

Tracing materials from "seabed to bedside" may therefore be challenging if good scientific practice is not followed. The examples in Annex 1 could be traced via the scientific and patent literature. Traceability could have been improved if, for instance, the location of the collection sites, identifiers and the current location of specimens collected had also been provided. What is clear is that, when compounds become the subject of commercial research, they are much more difficult to trace, given the confidential nature of the process. However, the pharmaceutical companies involved in the two examples authored comprehensive review articles that were used to compile the data presented in Annex 1.

Other types of benefit may also arise. For example, MGR research may:[14]

- Contribute to the conservation and sustainable use of MGR;
- Promote scientific research and facilitate the collection of/access to MGR;
- Build capacity to collect/ access and utilise MGR;
- Create and strengthen capacity to conserve and sustainably use MGR;
- Promote the sharing of benefits from MGR;
- Generate knowledge and technological innovation, facilitate development and enable the conduct of marine scientific research;
- Promote the development and transfer of marine technology.

Benefits that arise as the result of the use of MGR are therefore far broader and may have greater social and environmental impact, over longer timescales, than might be conferred by only requiring monetary benefit-sharing. An increased understanding of the marine environment arises from studying marine genetic resources, which can support and further the development of appropriate marine conservation and environmental protection measures.

2. The Marine Bioprospecting Process

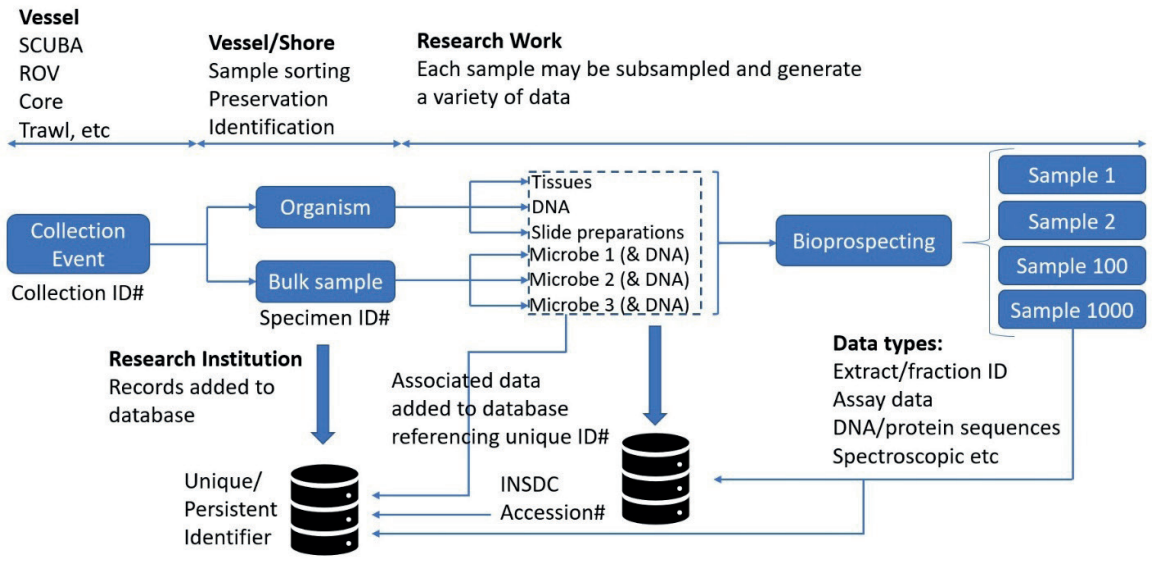
2.1 Data, sample processes and workflows in marine scientific research

To discuss traceability of MGR, it is helpful to set the scene on relevant data and sample processes and workflows in bioprospecting, including usage of identifiers (Figure 2). It should be noted that the processes described below apply equally to non-commercial and commercial research, the difference being that commercial enterprises will generally not share their specimens and data openly, although they may do this if they are part of an academic–industry collaboration (e.g. the EU Project PharmaSea, 2012-7).[15] However, rigorous standard operating procedures and data curation are also (generally) applied in industry to ensure that commercial decisions are based on validated data.

The starting point for bioprospecting is sample collection – whether through marine scientific research activities, or less commonly, through collections specifically for bioprospecting purposes. This may be shore-based collection or a cruise on a research vessel, with resulting collections of biological samples from different sampling events (such as scuba diving, trawls, benthic cores, remote operated vehicle collection, etc.). These sampling events are allocated a code or identifier. The resulting samples may be sorted at the shore-based or research vessel-based lab (or at a later stage at the research institute). Here, they may undergo preliminary identification to the highest taxonomic resolution possible[16] and preservation for further study, for example by genetic/genomic analysis. Generally, the specimens will be allocated with an identifier at this point – typically an in-house specimen code/number – unique within this context (locally unique). Bulk samples may also be preserved in their entirety (and allocated with an identifier), for later sorting of individual specimens, or collected as environmental samples (e.g. water or sediment samples) for genomic analysis.[17]

Back at the relevant institute/company, the records may be added to a database and the specimen allocated a "unique" or "persistent" identifier. Such identifiers must meet certain criteria to be valid – persistence, authority, discoverability and resolvability[18] (Guralnick et al., 2014, 2015). These identifiers allow for definitive resolution and identification of records, and communication and linkages between databases,

Figure 2. A general workflow covering both marine scientific research and the bioprospecting process, tracing the processes for samples/materials and data



such as between an in-house database and a global database/data aggregator.[19] Global standards are also critical to ensure data are FAIR (findable, accessible, interoperable and reusable)[20] and support traceability. The usage and development of global data standards in biological research, such as DarwinCore for biodiversity data and MIxS for sequence data, are covered in a recent review (Rabone et al., 2019).

During laboratory work, the specimens may be further analysed. As part of the process, subsampling often occurs – for example a tissue sample for extraction of DNA.[21] One specimen can lead to a multitude of resulting samples – tissues, DNA, slide preparations and many others – and some of these samples may in turn be subsampled – a "tree" of one-to-many relationships between the original "parent" specimen and the resulting "child" samples (Figure 2). These relationships are reflected in the records, where any resulting sample is linked to the original specimen – referencing its persistent identifier. In this way, even if many subsamples have been isolated (and many processing steps undertaken), the link back to the source or parent specimen can still be made. The Global Genome Biodiversity Network (GGBN) has developed data standards specifically to model and capture these sample relationships (Droege et al., 2016).

Results of lab work such as DNA sequences are stored in databases such as the International Nucleotide Sequence Database Collaboration (INSDC).[22] When sequences are deposited, they are allocated an identifier, known as accession numbers (ANs), unique within the INSDC system. These numbers are referenced in resulting publications, alongside specimen identifiers such as registration/accession numbers if the specimens are vouchered in a museum.[23] Many journals will not allow publication until evidence is provided that DNA sequence data has been deposited in the INSDC. In some cases, the persistent identifiers and/or the locally unique specimen identifier may also be included. As examples, the specimen tables in the following publications include these identifiers, provided also in DarwinCore archive supplementary files[24] (Glover et al., 2015; Dahlgren et al., 2016; Wiklund et al., 2017, 2019).

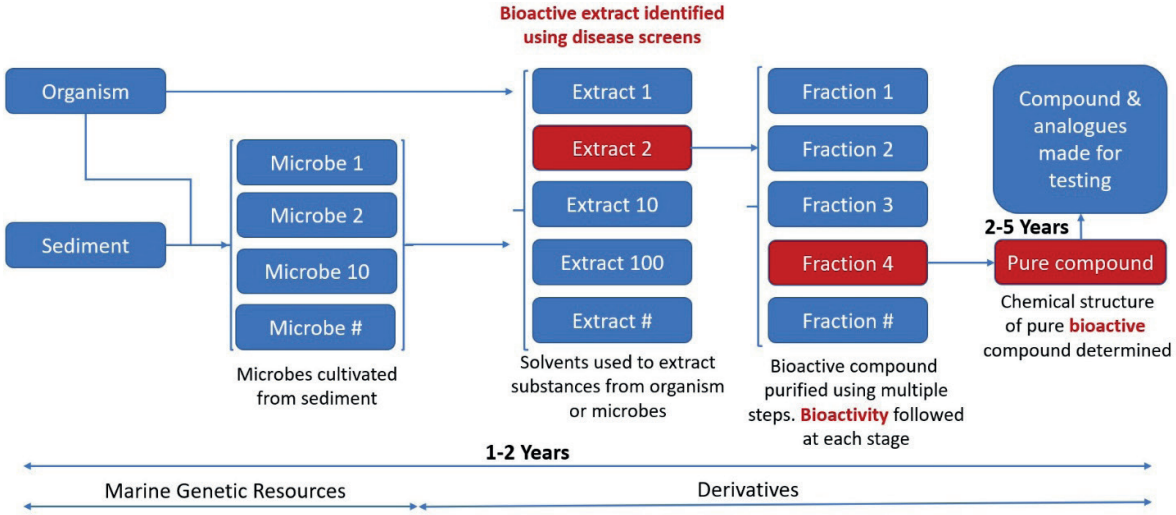
The usage of identifiers in databases and publications is key to the traceability of MGR samples/collections and data. The processes outlined above are what could be described as current best practice, and are described in detail in two recent reviews of marine scientific research/collection and analysis of MGR in the context of the proposed legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity in areas beyond national jurisdiction ("BBNJ Agreement") (Rabone et al., 2019; Rogers et al., 2021). A variety of approaches are discussed in sections 3.1-3.5, some with greater or lesser potential for traceability.

2.2 The bioprospecting pipeline

Once MGR have been obtained, the process of discovering potential commercial value can start – a process often involving chemical and biological expertise (Figure 3). There are two main routes by which biologically active ("bioactive") substances can be obtained. The first is to take a whole organism, typically an invertebrate, and to obtain a complex mixture of many substances, using chemical solvents; this is termed an "extract." The second is to take the organism, or a sediment sample, and isolate bacteria or fungi using microbiological techniques. These microbes can then be grown in vessels and extracts can be made as for whole organisms. These extracts are purified using a variety of processes to yield a pure compound, with typically two to five steps needed. This process may be guided by the bioactivity of the extracts and fractions using tests ("assays" or "screens") that indicate bioactivity against diseases. These assays can take a variety of formats, can be manual or automated, and often focus on human health indications, such as infectious/parasitic diseases, cancer, inflammatory conditions or central nervous system disorders, among others.

The discovery process is complex and, as described above for the research process, each sample along a pathway has the potential to generate multiple downstream subsamples and associated datapoints. It is easily possible therefore for a single organism or sediment sample to generate hundreds if not thousands of subsamples (Figures 2 and 3). It thus takes a great deal of effort to follow these materials from the organism/specimen to the pure, active compound, and often large spreadsheets, databases or dedicated laboratory information management systems are needed, and good data curation is essential.

Figure 3. A general workflow detailing stages of the bioprospecting process showing indicative timelines



Note: Each stage generates multiple downstream extracts/fractions/compounds, and extracts/fractions that have activity against human diseases (that are "bioactive") are followed through the process.

One issue often encountered is that these dedicated laboratory information management systems may not interact with the earlier part of the process (sampling, curation of material and related information, Figure 2). This means that tracing materials/samples accurately through this part of the process can be difficult without unique sample identifiers that follow the materials through each stage of the process (see Section 3.4).

When a pure compound with potent and selective bioactivity against one of these diseases is discovered, its chemical structure is determined. At this stage, the compound can be manufactured in larger quantities, and analogues made. A compound may also be altered structurally by chemists to make it more "drug-like" and simpler to produce, as was the case for Halaven (Box 1, Annex 1). At this stage, the commercial part of the process is formalised, often with the filing of patents on the compounds and their means of production, followed by extensive preclinical evaluation in animals, which may take several years, as described in Section 1.2 and Figure 1.

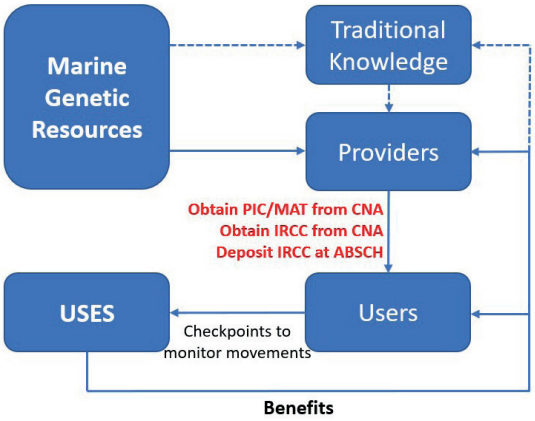
3. Traceability Policy Options and Implications

This section highlights that, in addition to the scientifically assigned identifiers and traceability infrastructure outlined above, governments may have ABS infrastructure and identifiers that are assigned for reasons related to traceability in the administrative or legal sense. Whereas scientific identifiers associated with a record are generally globally unique and persistent, allow linkage of information between databases (including across jurisdictions) and are relatively easy to retrieve, legal or administrative mechanisms and associated identifiers rarely share these attributes (Humphries et al., 2021b). This is partly because, although there is an international framework for ABS, national ABS measures differ in the implementation of authorisation (e.g. permits or registration), benefit-sharing (e.g. contracts), reporting and identifier mechanisms that are relevant to traceability. National ABS measures also differ in the way that the traceability policy options outlined below interact with scientifically assigned identifiers. For example, some measures incorporate or are complementary to, or are in addition to, scientific best practice for identifiers. This poses a significant challenge for the global traceability of MGR.

The Nagoya Protocol has a framework for ABS measures (Articles 5–8) and monitoring and compliance measures (Articles 15–18), described briefly below, which may assist in monitoring the collection, use and movement of genetic resources and associated traditional knowledge. Figure summarises the process.

- **PIC and MAT system**. Subject to domestic ABS measures, before accessing a genetic resource, PIC must be obtained from the Competent National Authority (CNA) and evidence provided that MAT have been negotiated in accordance with national laws. Permits and/or benefit-sharing agreements may contain information about the origin of the genetic resources or traditional knowledge as the starting point for traceability.
- **Obtaining of an IRCC and the role of CBD's ABS Clearing House (ABSCH)**.[25] The ABSCH can capture evidence of compliance with PIC and MAT. A country may publish some (or all) details of a permit or equivalent on the ABSCH, and this constitutes an IRCC. This may include information such as on the nature and location of the MGR, PIC/MAT and how the MGR may be used. The ABSCH assigns each record (including IRCC) an ABSCH unique identifier (UID). The information an IRCC contains may be stored in different ways by provider country, and it can be amended, and a revision number added.[26] However, its currency and accuracy depends on the capacity of each government to update information on the ABSCH.[27] This is effectively a system of pdfs without stable links between the record and relevant databases, so not a reliable source of where genetic resources are at any given time. This means that this is not a dependable or even a feasible means of tracking movement of the resources on their own. Only approximately 2,370 IRCCs are listed with the ABSCH at the time of writing.
- **Use of checkpoints to monitor movements**. The Nagoya Protocol requires ("as appropriate") States Parties to have checkpoints that collect information such as PIC/MAT/IRCC/MGR source and use. National implementation of checkpoints varies, and they may require a range of information at different stages of the bioprospecting process, from initial collection through research use to potential commercialisation. Such checkpoints include Intellectual Property (IP) offices, pharmaceutical regulatory agencies and bodies engaged in research.
- **User measures to capture movements across borders**. The Nagoya Protocol provides a framework for States Parties to develop user measures that deal with movements of MGR and data across borders. These measures aim to ensure user countries comply with provider country PIC/MAT and that parties to the protocol take effective measures to address situations of non-compliance with these requirements.

Figure 4. Steps to be taken to obtain legal certainty over MGR from within national jurisdiction



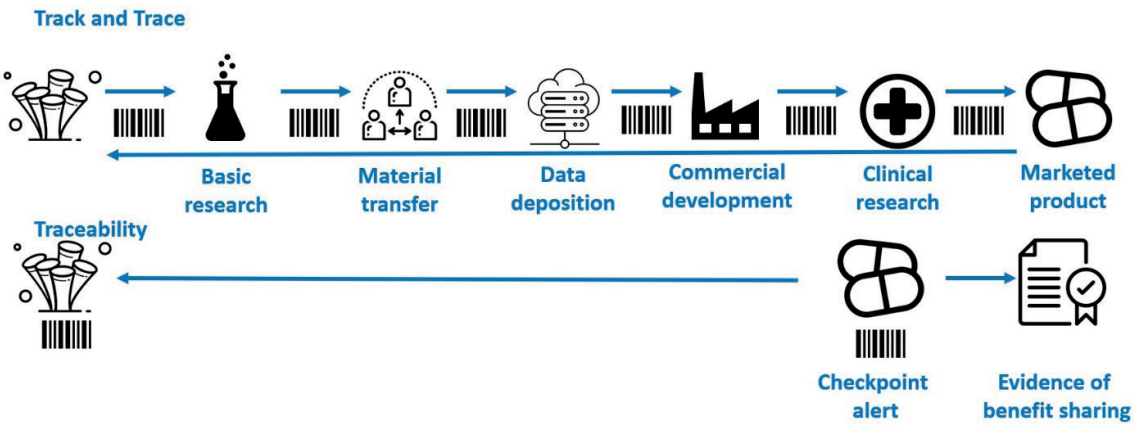
Note: Administrative steps in red.

This report makes a distinction between traceability and track and trace (Figure 5). In a track and trace system, for instance a parcel delivery system, once an order is placed, the progress of this and its exact location is known via the use of barcodes and checkpoints, so that it is clear where the parcel is at any moment in time and when it will be delivered. In a traceability system, such as a car recall system, the vehicle has a unique identifier when it leaves the factory. The exact location of the vehicle after it leaves the factory is not known. If a fault with the particular model of car is identified, the factory issues a recall notice, and the owner checks the unique identifier and contacts the factory to have the problem remedied. In this case, the end user (car owner) carries out due diligence to verify if their vehicle has the problem for which the recall notice was issued. In the same way, different systems for tracing MGR through the bioprospecting process may be considered. Elaborate systems could be developed to carry out full track and trace throughout the marine bioprospecting process, linking origin with eventual use and benefits, but these would be very costly and require intensive management and curation (Humphries et al., 2021b. A question remains as to whether such a system is justifiable economically. An alternative approach to traceability akin to the car recall system would require the use of unique identifiers and due diligence when the material changes hands.

Sections 3.1–3.5 discuss different approaches to traceability, including the merits and disadvantages of each. Box 2 summarises the current negotiations for the proposed legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity in areas beyond national jurisdiction (the BBNJ Agreement). Table 2 offers brief observations for each traceability approach based on the following three criteria: potential impact in terms of basic research, practicality in achieving traceability objectives and resourcing implications for individual states. Section 4 then uses these three criteria to frame the discussion about traceability approaches used in two case studies, on Fiji and South Africa.

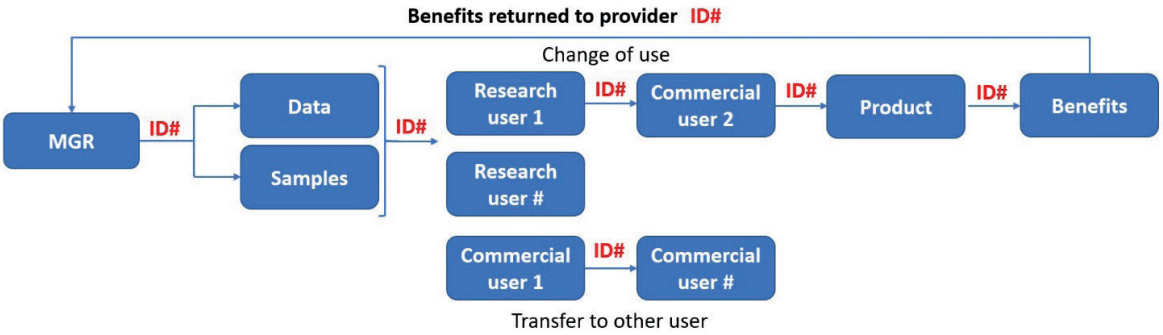
Not all traceability approaches in Section 3.1–3.5 use all of the traceability infrastructure under the CBD and Nagoya Protocol described above.

Figure 5. Comparing track and trace and traceability approaches



Note: The steps in the track and trace approach exemplify the types of processes involved in product development (see also Figures 1–3). Unique identifiers are indicated using bar codes. The figure is based on those in Humphries et al. (2021a). Graphics are from the Noun Project.

Figure 6. An example of how full track and trace might work



Note: When a MGR is accessed, a record is deposited in a central database, which provides a unique ID#. The database is updated at each step of the process, referencing the ID#. Notifiable events may include sample and data deposition in collections and international databases, transfer between users, change of use, publication and patent application. Once benefits are generated, they can be shared with the original provider of the MGR. Administrative steps in red.

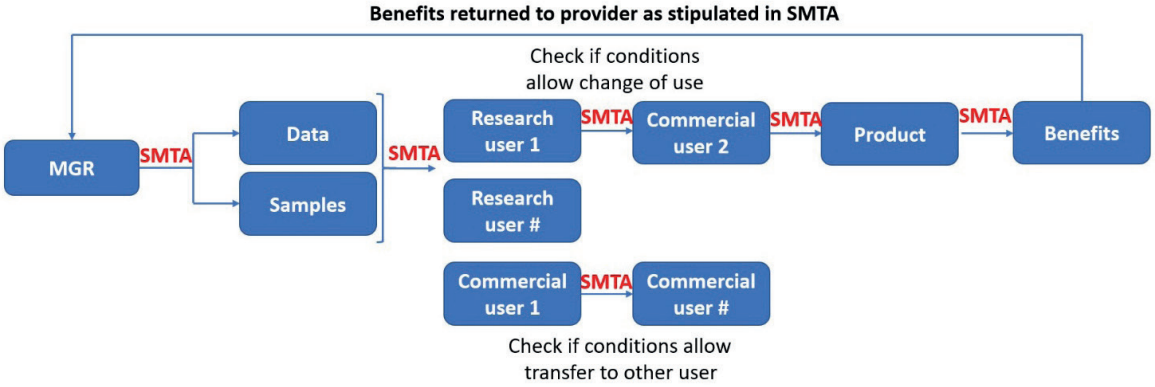
Similarly, different approaches may use the infrastructure in different ways. For example, a track and trace system (3.1) may place obligations for PIC and MAT, IRCC and checkpoint notifications throughout the research and development process, whereas an end user system (3.3) may engage this infrastructure at a later stage of the research and development process, as the following discussion indicates. The traceability schemes presented below also have different administrative and compliance burdens and deal differently with transfer of MGR between jurisdictions (Humphries et al., 2021b). Box 3 summarises technological solutions that may apply to several of these approaches to traceability.

3.1 Track and trace options

A full track and trace system has the potential advantage that every movement of the sample and/or information from user to user can be traced so that any uses or end products can, in theory, have a proven link to the original MGR and the provider country for the purpose of sharing benefits. It should be noted that, under the Nagoya Protocol, track and trace is not an explicit element of traceability. Opportunities and challenges for full track and trace systems are outlined below. Figure 6 indicates how track and trace might operate in practice and Table 2 includes observations about this approach in relation to the three criteria noted above.

- **Opportunities for full track and trace systems**. In principle, track and trace infrastructure assists countries to know where resources and knowledge are at any stage of the bioprospecting process at any timepoint, and how they are being used. Under national measures, this may be possible using reporting requirements, identifiers, checkpoints, change of use, third-party transfer provisions and other traceability mechanisms that follow the chain of custody of materials as they move from the place of origin and through the research, development and/or commercialisation process.
- **Challenges for full track and trace systems**. Often, different stages of the bioprospecting process occur in different countries, and it may be very difficult to track these across borders. The international checkpoint system under the Nagoya Protocol is meant to catch unauthorised movement of materials but in practice it is very *ad hoc* and has many gaps. Although the ABSCH should capture information updates, often information is unavailable or out of date, because of lack of user input for a variety of reasons. To remedy this and make a full track and trace system viable, an update to the ABSCH UID would be required at every step in the bioprospecting process, from original collection to eventual commercialisation by subsequent users in every jurisdiction in which the work is carried out. Elements of national track and trace systems vary significantly between countries, creating a lack of compatibility when materials traverse borders. Other challenges include a high compliance burden on the initial researchers (rather than commercial end users), which may deter basic research. More complex reporting/tracing requirements may

Figure 7. SMTAs as an example of contractual/licensing traceability options



Note: SMTAs may require that obligations are passed on to each subsequent user of the MGR, who must carry out due diligence to verify that PIC/MAT have been obtained, that transfer of materials to other users is permitted and that change of use is allowed. Once benefits are generated, the end user must return a share of these to the provider as stipulated in the SMTA. Administrative steps in red.

confuse users and create a disincentive for compliance, including updating checkpoints when notifiable events occur (e.g. change of use). Full track and trace systems represent a high-cost and resource-intensive option for governments when considering that most research on genetic resources is unlikely to produce commercial outcomes and benefits.

3.2 Contractual/licensing traceability options

One innovation of the ABS concept is that, while government administrative measures handle authorisation processes for the collection and use of MGR, benefit-sharing may be handled under contract law and negotiated directly between the provider and the user. However, traceability infrastructure under the Nagoya Protocol model tracks only PIC and MAT obtained under the national law of the provider country, and not whether users have complied with the terms of a benefit-sharing agreement or whether subsequent users or the genetic resources are similarly bound to benefit-sharing. Other mechanisms, such as Material Transfer Agreements (MTAs) and creative commons licences, may be attached to the movement of materials and information between users and can support traceability across jurisdictions. Opportunities/challenges for different options are described briefly below. Figure 7 outlines how MTAs might work in practice, and Table 2 includes observations about this approach in relation to the three criteria.

- **Opportunities for the use of Standard MTAs**. STMAs are used, for instance, in the multilateral system under the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA).[28] In this treaty, there is a list of plant species that are covered. The advantage of SMTAs is that they do not need to be negotiated for each movement of materials/information, but are based on standard terms that provide legal certainty to users, who can pass the burden of compliance with ABS obligations on to subsequent users of the MGR (if the original access authorisation allowed third-party transfer). Such contracts can stipulate the conditions to be observed on change of use and by any subsequent users if transfer is permitted. SMTAs may also require the recipient to carry out due diligence to check PIC and MAT have been obtained. SMTAs can include benefit-sharing provisions and will spell out consequences of breach of contract. Advantages of SMTAs include that they can be made machine-readable, aiding traceability, and that they reduce cost and time taken compared with case-by-case negotiations. Information is more difficult to define under agreements than samples but there are examples of data transfer agreements.[29] SMTAs may therefore be a useful part of a possible solution to traceability of MGR.
- **Opportunities for using creative commons licences**. This applies mainly to publications and data and information associated with genetic resources, such as DNA and protein sequence

data (DSI), maintained in well-curated interlinked databases. A creative commons licence would require those who deposit MGR-related data to DSI databases to also enter a standardised licence identifier that links to an online version of the licence. Different licence options are proposed; all would require DSI users to keep track of licences associated with DSI being used (WiLDSI, 2020). Such systems are already in operation for creative commons licences in science and requires interoperable databases and machine-readable identifiers.[30]

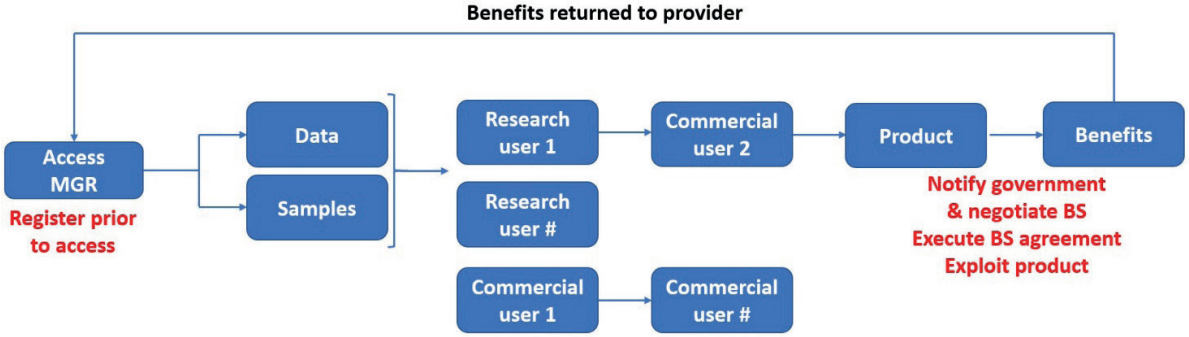
- **Challenges of contractual/licensing approaches to traceability**. The challenge with transferring the SMTA concept to MGR is that countries have not agreed on standard conditions under a multilateral system that are consistent across countries. Some countries, such as Kenya, have ABS laws that prescribe standard terms and conditions of MTA that can be adapted to suit a given transaction,[31] but few countries have this kind of guidance. Many countries preclude third-party transfers without authorisation of the government, which can increase cost and time for researchers. Users must have good data management procedures to maintain specimen/information movements and third-party transfers.

3.3 End product/end user traceability options

Compared with track and trace systems, these traceability options may not require the tracing of every movement of MGR and associated information between users. Instead, downstream users report on activities or products, at which point certain obligations such as reporting, disclosure or benefit-sharing obligations are triggered. Such systems may be "lighter" options and technical and administrative requirements may be less than for full track and trace options. Two examples of end user traceability systems and opportunities/challenges for these options are briefly described below. Figure 8 indicates how such an approach might work in practice and Table 2 includes observations about these options in relation to the three criteria.

- **Opportunities/challenges of end user traceability systems**. This is an example of an approach in which end users, such as researchers or organisations developing commercial genetic resource products or inventions, trigger traceability obligations rather than the initial researchers. There may be local laws relating to collection permits etc. that affect the initial researchers, but the obligations for reporting on and sharing the benefits from their use for research and development purposes are triggered only once economic exploitation arises. It is at that point that traceability infrastructure such as registers and identifiers are used to link the end use to the MGR origin and provider. End user approaches could take many forms. One is exemplified by Brazil's ABS law concerning its genetic heritage,[32] the description of which is beyond the scope of this paper but is outlined in Davis et al. (2016) and Belisário Zorzal et al. (2020). While end user approaches may incur less cost than full track and trace systems, resources and infrastructure (including checkpoints and databases) are still required to link the end use product or activity back to the original sample/information.

Figure 8. Example of how an end user traceability system could work



Note: Under this hypothetical example of how an end user traceability system could work, researchers may use genetic resources for research and development but, at the stage of commercialisation, the government must be notified and benefit-sharing conditions agreed. Only the end user is responsible for ensuring benefit-sharing occurs. Administrative steps in red.

Table 2. Summary of potential impact with regard to basic research, practicality for achieving traceability objectives and costs for individual states of the different traceability systems outlined in Sections 3.1–3.5

Traceability approach	Potential impact for basic research[48]	Practicality for achieving traceability objectives	Resourcing implications for individual states
3.1 Track and trace options (No complete systems in place in any country, although some countries' measures may have elements.)	High – reporting and compliance burden mostly placed on the initial user and not end user and may hinder basic research.	Low – different requirements between states with incompatible systems may mean that tracing MGR across borders is difficult if not impossible.	High – requires national level IT systems/database development to record MGR location, change of use and movement across borders, with users potentially required to show compliance at each step. Costs include both upfront/setup and ongoing/maintenance.
3.2 Contractual/ licensing traceability options (SMTAs are used as part of the ITPGRFA. SMTAs are used in Kenya.)	Medium – similar burden for users and subsequent users at all steps of the research, development and commercialisation process.	Medium – practical to manage under national laws (e.g. contract and IP laws) but user engagement with traceability may improve if there are standard terms and conditions (no globally agreed approach yet for MGR). Users must have good data management procedures in place to keep track of samples and data to enable any eventual product to be traced back to the original MGR.	Medium – mostly managed under private law but traceability outcomes would improve if government was involved in building capacity and guidelines for standard terms and conditions.
3.3 End user traceability options (Used in Brazil)	Low – compliance burden is mostly on the end users of materials and information.	Medium – practical if there are mechanisms in place (e.g. registration) where end use can be linked to the original sample/ information.	Medium/high – costs and resources required for traceability infrastructure, requires significant database and IT systems development; lower than track and trace, however, as monitoring required only at end use. Costs include both upfront setup and ongoing maintenance.
3.3 End product traceability options (Several countries, such as India and Vanuatu, have advocated for declaration of origin in patents.)	Low – obligations fall primarily on commercial researchers and end users.	Low – only useful if national IP systems develop common standards and have better connectivity between databases.	High – requires both legislative amendments and database development/upgrades to improve linkages between databases. Costs include both upfront setup and ongoing maintenance.
3.4 Existing open access traceability options (For DSI, infrastructure is global and well developed. For samples, repositories are becoming increasingly connected.)	Medium – burden placed on the initial user and not end user. Follows existing best scientific practices.	High – many MGR databases and sample repositories are already well connected and apply the FAIR principles, meaning that traceability should be possible.	Low – low cost to government (substantial costs are borne by the sample and data repositories). No legislative amendments/ regulations required as a status quo option but government awareness and support for open access frameworks needed.
3.5 Combined traceability approaches (There is little empirical evidence about whether countries are considering combined approaches to traceability and what these combinations are.)	Approach selects elements from each of the above systems to create a hybrid system that is tailored to the capacity and needs of each state. Would need to be developed with a clear traceability strategy.		

- **Opportunities/challenges of end product approaches such as IP disclosure of origin**. Several countries, including India and Vanuatu, have advocated for a minimum standard across national IP laws that requires patent applications to disclose the origin of MGR incorporated in an invention.[33] Patents allow the holder to commercialise an invention and prevent others from using it without their permission. The idea is that, by increasing transparency through disclosure, patent systems could monitor the incorporation of genetic resources and traditional knowledge in patented inventions, which may help link the end product with the provider countries that may be entitled to benefits from their use. Disclosure of origin combined with other traceability mechanisms, including unique identifiers and patent office checkpoints, could support traceability across jurisdictions. However, the examples in Annex 1 show the complexity of patents associated with MGR-derived products. While the original MGR-derived compound may be the subject of an initial patent with a declaration of origin, further developments, such as generation of analogues and means of production, may not refer directly to the origin of the MGR, thus hindering traceability. To determine to what extent a product contains MGR would require an investigation in each country where a patent may have been claimed, as patents are enforced under national laws. This would make traceability using IP challenging, particularly as some countries may decide not to require disclosure of origin (and patents are likely to be filed in jurisdictions different from the collection country). Requiring a declaration of origin in MGR patents may not capture certain products such as breeding stock, cosmetics and nutraceuticals, which are often not the subject of patents. Although IP systems exist in most countries, issuing IP as a mechanism for ABS traceability would require the currently disparate and poorly integrated national patent databases to be an order of magnitude more accessible, harmonised and, ideally, integrated globally.

3.4 Existing open access traceability options

Traceability in science involves two components – traceability of MGR data (both DSI and specimen records in global data aggregators such as the Ocean Biodiversity Information System (OBIS) and the Global Biodiversity Information Facility (GBIF), and taxonomic information in the World Register of Marine Species (WoRMS);[34] and traceability of the physical samples themselves. Here, the usage of open access databases and repositories and how they might be used to trace the movement of both data and physical samples is described. Section 2.1 and Figure 2 presented much of the infrastructure needed and existing traceability mechanisms. Table 2 offers brief observations on this approach using the three criteria.

- **MGR databanks**. The INSDC[35] is formed of three international databanks (US, EU, Japan) that contain millions of DNA and protein sequences as well as a great deal of other information. The databases regularly share information and receive around 10 billion requests per year. Open access is built into their fabric, and journals publishing findings of genetic/genomic studies require an AN as proof that a sequence has been deposited in the INSDC prior to publication. When depositing sequence data, there are fields (e.g. country tag and geographic coordinates) available to record locality (therefore indicating the "origin" of the MGR), where relevant. The machine readable ANs may be used to link the MGR to other data sources.
- **Physical MGR samples in natural history collections**. Biological collections in museums and biorepositories are available for scientific research. The use of unique identifiers for physical samples was discussed in Section 2.1 showing how these aid tracing movement of samples during the scientific process. Better linkages between INSDC and biodiversity databases (where natural history collections specimen records are generally published) linking a specimen record with an AN would further support traceability, but this would require significant additional funding for database development and maintenance. GGBN also facilitates sharing of genetic resources held by its partners and has

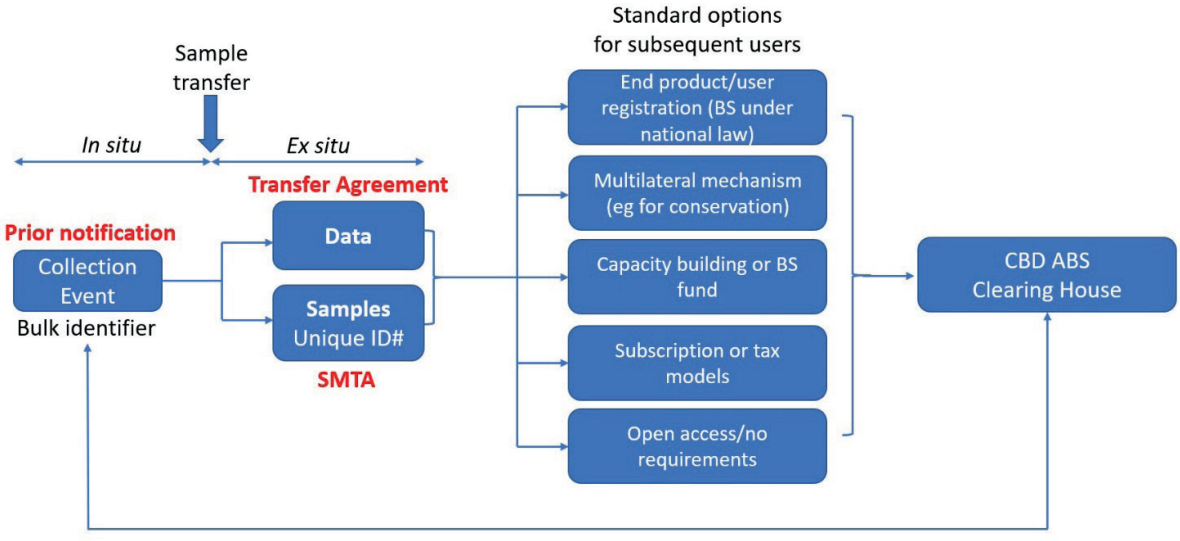
developed standard MTAs and data standards that capture PIC/MAT and therefore traceability of compliance.[36]

- **Physical MGR samples for bioprospecting research**. Several collections exist globally that allow access to MGR for bioprospecting, including the US National Cancer Institute (NCI) Natural Products Branch Open Repository,[37] Norway's Institute for Marine Research (Marbank)[38] and Australia's Naturebank.[39] Each has different contractual terms to access the MGR under an MTA. The US NCI's collection is obtained from many countries under its "Letter of Collection"[40] and permits users to access the materials under an SMTA without cost to the user.[41] The NCI does not track the movement of samples during the research and development process but requires citing of the source country and NCI sample identifier in publications. Benefit-sharing agreements must be signed with the source country before commercial sale of any products derived from research on the MGR. This process requires user compliance to link any benefits back to the origin of the MGR.
- **Opportunities and challenges to open access traceability options**. The main opportunity is that this builds on existing scientific infrastructure such as the INSDC, which is encouraging users to include the country tag where relevant.[42] This data infrastructure is widely available and free to users, and research norms have developed where deposition of data is expected soon after it is generated. Infrastructure and networks to connect physical sample collections are well established in some cases and being further developed in others.[43] However, if all collections were to be made discoverable and accessible, additional funding and a global-scale initiative would be required (for elaboration see Collins et al., 2020).

3.5 Combined traceability approaches

Countries need not take a one-size-fits-all approach, and could combine different strategies, including those described in Sections 3.1–3.4. Traceability approaches can be tailored to the type of resource or activity being carried out with it. Monetary benefits could be traced via an end user/end product traceability option as described in Section 3.3. Much of this builds on good scientific practice as described in Section 3.4. There have been several proposed combined approaches to traceability, such as suggested by Broggiato et al. (2018) in their chapter, *Mare Geneticum*, which requires "Obligatory Prior Electronic Notification" before collection of MGR can start. Alternatively, the Tiered Approach uses tiers of activities, each

Figure 9. Elements that might be used to make a combined approach to traceability of MGR



Note: The ABSCH receives information on the standard option applied and uses the bulk identifier and sample unique identifier to link it back to the collection event and location. Figure adapted from Humphries et al. (2021b). Administrative steps in red.

Box 2. Implications for BBNJ and the proposed approach to traceability in the 2019 draft text

An internationally legally binding instrument to the United Nations Convention on the Law of the Sea is being negotiated to cover the conservation and sustainable use of biodiversity of areas beyond national jurisdiction ("the BBNJ Agreement"). MGR and the modalities of benefit-sharing represent one of the main elements of the agreement. This will be a multilateral system, and therefore different from the Nagoya Protocol, in which a bilateral relationship exists between the provider and user countries. The current draft text (United Nations General Assembly, 2019) includes potential obligations regarding access to and utilisation of MGR, sharing of benefits, monitoring and IP. A clearing house mechanism has been proposed that would collect information from MGR users about the collection activity, sampling locations and where samples are stored. Samples are proposed be stored in collections and data archived in open source platforms. Current options for traceability in the draft text include the use of (legal) identifiers for MGR (in situ/ex situ/in silico) but currently the burden of the proposed system falls on the initial user and not the end user of the MGR. The initial user would have ongoing reporting obligations as well as being required to assign unique identifiers and make samples and data available in open access collections and databases. It is currently unclear what benefits might arise from such a system, and how these might be shared with countries.

with traceability requirements: collection of MGR; activities using physical samples; activities using DSI; access to and use of traditional knowledge; and conservation of MGR (Humphries et al., 2020). Elements that might be incorporated in a combined traceability approach are shown in Figure 9 and summarised in Table 2.

Combined traceability systems may require notification prior to a collection event, similar to in the Brazilian approach discussed in Section 3.3. This would require a national government to develop a specific web-based system for this purpose, which might necessitate the input of information on the nature of the activity proposed, researchers, research aims, geographical location, etc. When MGR samples are collected, unique identifiers need to be assigned and recorded on the web-based system. There may be a requirement to update the web-based system when new information is acquired (e.g. taxonomic identification, DSI), or when certain events occur, such as sample transfer or filing of a patent application. When data transfer occurs, this should be accompanied by a transfer agreement; samples should be covered by an SMTA (see Section 3.2).

A series of possible options would be available to subsequent users of the MGR or data derived from them. This could include end product/end user registration (Section 3.3), and monetary benefit-sharing should occur on the generation of commercial income and could be set as a fixed percentage by sector (e.g. pharmaceuticals, cosmetics). These percentages would need to be agreed between the national government and the industry sectors.

Another option is the use of a multilateral mechanism with benefits targeted at conservation measures. Registration on a capacity-building database similar to the ABSCH could be an additional requirement of any option, and this could be managed via the web-based system. The open access options discussed in Section 3.4 might be a viable mechanism for encouraging basic scientific research.

Subscription or tax models have been discussed for the use of DSI in basic scientific and commercial research; these are discussed in detail elsewhere (WiLDSI, 2020). All of these options require due diligence by subsequent scientific or commercial users to ensure legal certainty over the MGR being used.

Box 3. Potential of technological solutions for traceability

In February 2021, the United Nations Development Programme (UNDP)–Global Environment Facility (GEF) Global ABS Project initiated a pilot project between UNDP and PricewaterhouseCoopers (Turkey and India) to build methodology and guidelines for implementing traceability and benefit-sharing through blockchain technology.[49] Recent reports discuss the significant challenges involved in implementation and futureproofing for blockchain in detail (Morgera et al., 2020; Oldham, 2020; WiLDSI, 2020). Countries require technological capacity to use the blockchain, as well as user compliance to update the system at every stage of the process, requiring capacity-building and substantial upfront investment and costs. One unintended consequence of the technology could be possible restrictions on currently open access data (WiLDSI, 2020). A technological solution would ideally need to build on existing scientific data infrastructure. An alternative would be to use blockchain adaptors for existing data and sample repository identifiers rather than developing a stand-alone blockchain system. Blockchain technologies have been applied in the fisheries context to trace the movements of fish from harvest to plate,[50] and there are already initiatives that use blockchain for genetic resources.[51] However, it is unclear whether national governments are using these for MGR bioprospecting traceability purposes.

4. Case Studies: Fijian and South African Traceability Systems

There need not be a one-size-fits all approach to traceability mechanisms. Diverse approaches that suit local research and development environments can achieve similar traceability outcomes. To illustrate this, two case studies, of Fiji[44] (which uses contractual and open access approaches to traceability) and South Africa[45] (which uses elements of the track and trace and contractual approaches to traceability) are briefly discussed below. The lessons learnt from the two countries show that the informal system in Fiji suits local conditions because of the highly personal nature of interactions, whereas South Africa demonstrates a prescriptive approach to ABS laws. The analysis offers brief observations for the two approaches based on the three criteria from Table 2: potential impact for basic research, practicality for achieving traceability objectives and resourcing implications. Please refer to the separately published Commonwealth Secretariat case studies for further information.

4.1 Potential impact for basic research

The Fijian system relies on a database and spreadsheets and encourages basic research. Although no commercial products have made it to market to date, there has been a large amount of research published on Fijian MGR, and several compounds derived from these have made it as far as human clinical trials. International collaborations have enabled the creation of physical research infrastructure, a taxonomic sample repository and a database containing valuable information on Fijian MGR. The system is highly personal and collaborative and, although there are agreements and permits to obtain, it works well because of the low overall volume of research carried out by international researchers in Fiji. Export permits are normally granted in less than one month. The impact for basic research is low.

While the South African system simplifies discovery bioprospecting research by only requiring a notification to be filed prior to collection of MGR, international collaborations may be hampered by the need to obtain an export permit, which can take a year or more. Exports of MGR, or derivatives to be used for bioprospecting, must be accompanied by an MTA and a benefit-sharing agreement. This administrative burden is placed on the initial researchers and technology transfer offices of research institutions involved. A lengthy status report also needs to be completed on an annual basis for discovery and commercial bioprospecting. A positive outcome for basic research of the South African biodiversity legislation is the creation of the National Biobanks Initiative, funded by Germany, which will curate collections of South African species, including marine species, and make the database searchable globally via GBIF.

4.2 Practicality for achieving traceability objectives

The Fijian system currently works well in terms of achieving traceability, using an annual update system whereby all researchers, including international researchers, are required to file information on how the MGR have been used and to list papers published and any patent applications filed. However, multiple identifiers referring to the same sample can make tracing through the bioprospecting process challenging, albeit still achievable. The system relies on the personal nature of the interactions between researchers and government officials, which will not be scalable if MGR-based research increases significantly. The current system is also susceptible to disruption when staff changes occur or collaborative research funding is lost.

The South African system of annual status reports applies to the discovery and commercial phases of bioprospecting and captures relevant information such as biological resources collected, research

conducted, progress towards commercialisation, patent applications, engagement with industry, patent licensing, transfer of materials and any revenues generated. Scientific publications, a useful source for tracing materials, are potential benefits in the South African legislation. Detailed export permissions together with MTA and benefit-sharing agreements enable traceability of materials to researchers or companies in other countries.

4.3 Resourcing implications

Resourcing requirements for the current Fijian system are minimal, with government and university administrators in Fiji and international partners charged only with keeping track of the terms of the research agreements, memoranda of understanding and export permits. The annual reporting system is straightforward and mainly uses data that should be available as part of good scientific practice in the collaborating research institutions. The Fijian government's proposed formalising of the system will likely increase resourcing implications for the Ministry of Fisheries and Forestry, which is responsible for implementing the Nagoya Protocol in Fiji.

The Department of Environment, Forestry and Fisheries of the South African government has expended significant effort in developing extensive policies, administrative procedures, documentation[46] and a website[47] for bioprospecting. The system relies on a series of forms to be completed by the researchers and their institutional technology transfer offices or the commercial entity involved, after which the Department of Environment, Forestry and Fisheries issues a permit. For commercial bioprospecting, a benefit-sharing agreement must be negotiated with stakeholders; this can take considerable time and effort. Obtaining export permissions also comes with significant paperwork and wait times of sometimes over a year. The annual reporting for both types of bioprospecting is extensive and, although most of the questions are appropriate for the commercial phase of bioprospecting, many are premature for the discovery phase. This adds up to significant administrative burden for both researchers and the Department of Environment, Forestry and Fisheries.

5. Conclusions

There are no existing solutions for traceability that meet all the requirements discussed in this report. Full track and trace, while theoretically achievable, is complex, requiring substantial systems development and maintenance; is very resource-intensive; and requires co-ordination across different disciplines, from marine scientific research and informatics to law and policy. A bespoke track and trace system is likely to be costly, will take years to develop and may face resistance and limited uptake from users. Future financial gains from bioprospecting are very uncertain and may not cover the costs associated with a full track and trace system.

Approaches with a greater chance of success include those covered in Sections 3.1–3.4, elements of each of which national governments could use to develop a locally relevant combined approach to traceability, as discussed in Section 3.5. These approaches build on existing global infrastructure or can use procedures developed under other policy instruments. There are existing scientific networks that can support traceability, particularly in terms of databases, such as the INSDC for DSI and OBIS for species information. Many of these are supported financially by national governments, blocs or United Nations bodies (US, Japan, the EU for the INSDC, the Intergovernmental Oceanographic Commission for OBIS) but long-term funding for these is not always assured.

Some countries have established MGR sample repositories that provide important baseline taxonomic information about local species. Most repositories have local specimen databases; when developing these for use in a traceability system, the data should be available in accordance with the FAIR principles. However, a national sample repository is not a requirement for the development of a traceability system, and samples could be archived through engaging in local, regional or global collaborations such as GBIF.

Efforts to co-ordinate bioprospecting on MGR in a region should be encouraged, as should initiatives that make MGR data available ,openly as this will advance scientific development and understanding of marine biodiversity.

Acknowledgements

The authors wish to thank Chris Lyal, Natural History Museum, for helpful comments on the draft report. The cartoon figures used in Figures E1, 2 and 5 are from the Noun Project (coral by Nook Fulloption, liquid by Smalllike, database by Flatart, third party by Priyanka, drug by Adindar, certificate by Libertetstudio, factory by Iconsphere, and barcode by Adned Kadri).

References

Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources (2020a) "Combined Study on Digital Sequence Information in Public and Private Databases and Traceability". Convention on Biological Diversity, Montreal, 17–20 March. www.cbd.int/doc/c/1f8f/d793/57cb114ca40cb6468f479584/dsi-ahteg-2020-01-04-en.pdf

Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources (2020b) "Report of the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources". Convention on Biological Diversity, Montreal, 17–20 March. www.cbd.int/doc/c/ba60/7272/3260b5e396821d42bc21035a/dsi-ahteg-2020-01-07-en.pdf

Aicher, T.D., Buszek, K.R., Fang, F.G., Forsyth, C.J. et al. (1992) "Total Synthesis of Halichondrin B and Norhalichondrin B". *Journal of the American Chemical Society* 114: 3162–3164.

Belisário Zorzal, P., Curi Hauegen, R. and Pires Pimenta, F. (2020) "Biodiversity and the Patent System: The Brazilian Case". *Journal of Intellectual Property Law & Practice* 15(10): 829–837.

Bolton, J.J., Davies-Coleman M.T. and Coyne, V.E. (2013) "Innovative Processes and Products Involving Marine Organisms in South Africa". *African Journal of Marine Science* 35: 449–464.

Broggiato, A; Vanagt, T; Lallier, LE; Jaspars, M; Burton, G and Muyldermans, D, (2018) "Mare Geneticum: Balancing Governance of Marine Genetic Resources International Waters" *International Journal of Marine and Coastal Law* 33: 3-33

Collins, J., Rabone, M., Vanagt, T., Amon, D.J. et al. (2020) "Strengthening the Global Network for Sharing of Marine Biological Collections: Recommendations for a New Agreement for Biodiversity Beyond National Jurisdiction". *ICES Journal of Marine Science* fsaa227, doi:10.1093/icesjms/fsaa227

Conference of the Parties to the Convention on Biological Diversity Serving as the Meeting of the Parties to the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization (2014) "Implementing the Nagoya Protocol in Microbiology: Gaining Trust Building Trust". Pyeongchang, 13–17 October. https://www.cbd.int/doc/meetings/abs/np-mop-01/information/np-mop-01-inf-08-en.pdf

Cuevas, C. and Francesch, A. (2008) "Development of *Yondelis (trabectedin*, ET-743). A Semisynthetic Process Solves the Supply Problem". *Natural Product Reports* 26: 322–337.

Dahlgren T, Wiklund H, Rabone M, Amon D, Ikebe C, Watling L, Smith C, Glover A (2016) Abyssal fauna of the UK-1 polymetallic nodule exploration area, Clarion-Clipperton Zone, central Pacific Ocean: Cnidaria. Biodiversity Data Journal 4: e9277. https://doi.org/10.3897/BDJ.4.e9277

Davis, K., Holanda, P., Lyal, C., da Silva, M. and Fontes, E.M.G. (2016) "Implementation of the Nagoya Protocol on Access and Benefit Sharing". Dialogue between Brazil and the EU–Brazil Sector Dialogues Support Facility. doi:10.13140/RG.2.2.36253.31201

Droege, G., Barker, K., Seberg, O., Coddington, J.A. et al. (2016) "The Global Genome Biodiversity Network (GGBN) Data Standard Specification. Database 2016:baw125". doi:10.1093/database/baw125

EU (European Union) (2021) "Guidance Document on the Scope of Application and Core Obligations of Regulation (EU) No 511/2014 of the European Parliament and of the Council on the Compliance Measures for Users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation in the Union". https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.C_.2021.013.01.0001.01.ENG&toc=OJ%3AC%3A2021%3A013%3ATOC

Glover, A.G., Wiklund, H., Rabone, M., Amon, D.J., Smith, C.R., O'Hara, T., Mah, C.L. and Dahlgren, T.G., 2016. Abyssal fauna of the UK-1 polymetallic nodule exploration claim, Clarion-Clipperton Zone, central Pacific Ocean: Echinodermata. *Biodiversity Data Journal*, (4).

Glover, A. G., Wiklund, H., Chen, C., & Dahlgren, T. G. (2018). Point of view: managing a sustainable deep-sea 'blue economy'requires knowledge of what actually lives there. *Elife*, *7*, e41319.

Guralnick, R.P., Cellinese, N., Deck, J., Pyle, R.L. et al. (2015) "Community Next Steps for Making Globally Unique Identifiers Work for Biocollections Data". *ZooKeys* 494: 133–154.

Guralnick, R., Conlin, T., Deck, J., Stucky, B.J. and Cellinese, N. (2014) "The Trouble with Triplets in Biodiversity Informatics: A Data-Driven Case against Current Identifier Practices". *PLoS ONE* 9(12): e114069. doi:10.1371/journal.pone.0114069

Hirata, Y. and Uemura, D (1986) "Halichondrins – Antitumor Polyether Macrolides from a Marine Sponge". *Pure & Applied Chemistry* 58: 701–710.

Humphries, F., Gottlieb, H.M., Laird, S., Wynberg, R. et al. (2020) "A Tiered Approach to the Marine Genetic Resource Governance Framework under the Proposed UNCLOS Agreement for Biodiversity beyond National Jurisdiction (BBNJ)". *Marine Policy* 122: 103910.

Humphries, F., Laird, S., Wynberg, R., Morrison, C. et al. (2021a) "Draft Survey of Access and Benefit-Sharing Country Measures Accommodating the Distinctive Features of Genetic Resources for food and Agriculture and Associated Traditional Knowledge". Intergovernmental Technical Working Group on Aquatic Genetic Resources for Food and Agriculture, 3rd Session, Item 6, 1–3 June 2021 (GRFA/WG-AqGR-3/21/Inf.12).

Humphries, F., Rabone, M. and Jaspars, M. (2021b) "Traceability Approaches for Marine Genetic Resources under the Proposed Ocean (BBNJ) Treaty". *Frontiers in Marine Science* 8: 430. doi:10.3389/fmars.2021.661313

Kuznetsov, G., TenDyke, K., Towle, M.J., Cheng, H. et al. (2009) "Tubulin-Based Antimitotic Mechanism of E7974, a Novel Analogue of the Marine Sponge Natural Product Hemiasterlin". *Molecular Cancer Therapeutics* 8: 2852.

Morgera, E., Switzer, S. and Geelhoed, M. (2020) "Possible Ways to Address Digital Sequence Information – Legal and Policy Aspects". Report commissioned by the European Commission: ENV.F.3/SER/2019/6175145.

Newman, D.J. (2021) "Natural Product Based Antibody Drug Conjugates: Clinical Status as of November 9, 2020". *Journal of Natural Products* 84: 917–931.

Newman, D.J. and Cragg, G.M., (2020) "Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019". *Journal of Natural Products* 83: 770–803.

Oldham, P. (2020) "Digital Sequence Information – Technical Aspects". https://ec.europa.eu/environment/nature/biodiversity/international/abs/pdf/Final_Report_technical_aspects_of_DSI.pdf

Pettit, G.R., Inoue, M., Kamano, Y., Herald, D.L. et al. (1988) "Isolation and Structure of a Powerful Cell Growth Inhibitor Cephalostatin 1". *Journal of the American Chemical Society* 110: 2006–2007.

Rabone, M., Harden-Davies, H., Collins, J.A., Zajderman, S. et al. (2019) "Access to Marine Genetic Resources (MGR): Raising Awareness of Best-Practice through a New Agreement for Biodiversity Beyond National Jurisdiction (BBNJ)". *Frontiers in Marine Science* 6: 520. doi:10.3389/fmars.2019.00520

Rinehart Jr, K.L., Shaw, P.D., Shield, L.S., Gloer, J.B. et al. (1981) "Marine Natural Products as Sources of Antiviral, Antimicrobial and Antineoplastic Agents". Pure & Applied Chemistry 53: 795–817.

Rinehart Jr, K.L., Holt, T.G., Fregeau, N.L., Stroh, J.G. et al. (1990) "Ecteinascidins 729, 743, 745, 759A, 759B and 770; Potent Antitumor Agents from the Caribbean Tunicate *Ecteinascidia turbinate*". *Journal of Organic Chemistry* 55: 4512–4515.

Rogers, A.D., Baco, A., Escobar-Briones, E., Gjerde, K. et al. (2021) "Marine Genetic Resources in Areas Beyond National Jurisdiction: Promoting Marine Scientific Research and Enabling Equitable Benefit Sharing". *Frontiers in Marine Science* 8: 667274.

Rudy, A., López-Antón, N., Dirsch, V.M. and Vollmar, A. M. (2008) "The Cephalostatin Way of Apoptosis". *Journal of Natural Products* 71: 482–486.

Sigel, M.M., McCumber, L.J., Hightower, J.A., Hayasaka, S.S. et al. (1983) "*Ecteinascidia turbinata* Extract Activates Components of Inflammatory Responses throughout the Phylogenetic Spectrum". *American Zoologist* 23: 221–227.

Silvestri, L., Sosa, A., McKay, F., Diniz Vitorino, M. et al. (2020) "Implementation of Access and Benefit-Sharing Measures Has Consequences for Classical Biological Control of Weeds". *BioControl* 65: 125–141.

Simpkin, V.L., Renwick, M.J., Kelly, R. and Mossialos, E. (2017) "Incentivising Innovation in Antibiotic Drug Discovery and Development: Progress, Challenges and Next Steps". *The Journal of Antibiotics* 70(12): 1087–1096.

Sink, K.J., van der Bank, M.. Majiedt, P., Harris, L. et al. (2019) "Technical Report 4: Marine Realm". South African National Biodiversity Assessment 2018. Pretoria: South African National Biodiversity Institute.

Tabudravu, J., Morris, L.A., Kettenes-van den Bosch, J. and Jaspars, M. (2001) "Wainunuamide, a Histidine-Containing Proline-Rich Cyclic Heptapeptide Isolated from the Fijian Marine Sponge *Stylotella aurantium*". *Tetrahedron Letters* 42: 9273–9276.

Talpir, R., Benayahu, Y., Kashman, Y., Pannell, L. and Schleyer, M. (1994) "Hemiasterlin and Geodiamolide TA; Two New Cytotoxic Peptides from the Marine Sponge *Hemiasterella minor* (Kirkpatrick)". *Tetrahedron Letters* 35: 4453–4456.

Tiller, R., De Santo, E., Mendenhall, E., Nyman, E. and Ralby, I. (2020) "Wealth Blindness beyond National Jurisdiction". *Marine Pollution Bulletin* 151: 110809.

The Royal Society (2017) *Future Ocean Resources: Metal-Rich Minerals and Genetics – Evidence Pack.* London: The Royal Society.

United Nations General Assembly (2019) "Revised Draft Text of an Agreement under the United Nations Convention on the Law of the Sea on the Conservation and Sustainable Use of Marine Biological Diversity of Areas beyond National Jurisdiction". A/CONF.232/2020/3, 18 November.

White, K.N., Tenney, K. and Crews, P. (2017) "The Bengamides: A Mini-Review of Natural Sources, Analogues, Biological Properties, Biosynthetic Origins, and Future Prospects". *Journal of Natural Products* 80: 740–755.

Wiklund H, Taylor JD, Dahlgren TG, Todt C, Ikebe C, Rabone M, Glover AG (2017) Abyssal fauna of the UK-1 polymetallic nodule exploration area, Clarion-Clipperton Zone, central Pacific Ocean: Mollusca. *ZooKeys* 707: 1–46. https://doi.org/10.3897/zookeys.707.13042

Wiklund H, Neal L, Glover AG, Drennan R, Rabone M, Dahlgren TG (2019) Abyssal fauna of polymetallic nodule exploration areas, eastern Clarion-Clipperton Zone, central Pacific Ocean: Annelida: Capitellidae, Opheliidae, Scalibregmatidae, and Travisiidae. *ZooKeys* 883: 1–82. https://doi.org/10.3897/zookeys.883.36193

WiLDSI (Scientific Approaches for Digital Sequence Information) (2020) "Finding Compromise on ABS and DSI in the CBD: Requirements and Policy Ideas from a Scientific Perspective". Bonn: BMBF.

Wilkinson, M., Dumontier, M., Aalbersberg, I. et al. "The FAIR Guiding Principles for Scientific Data Management and Stewardship". *Sci Data* 3: 160018 (2016). https://doi.org/10.1038/sdata.2016.18

WIPO (2020) *Key Questions on Patent Disclosure Requirements for Genetic Resources and Traditional Knowledge*. 2nd ed. Geneva: World Intellectual Property Organization.

Wright, A.E., Forleo, D.A., Gunawardana, G.P., Gunasekera, S.P. et al. (1990) "Antitumor Tetrahydroisoquinoline Alkaloids from the Colonial Ascidian *Ecteinascidia turbinate*". Journal of Organic Chemistry 55: 4508–4515.

Yu, M.J., Zheng, W. and Seletsky, B.M. (2013) "From Micrograms to Grams: Scale-Up Synthesis of Eribulin Mesylate". *Natural Product Reports* 30: 1158–1164

Annexes

Annex 1

MGR Examples – the Path from Discovery to Clinical Application

Yondelis - marine ascidian-derived pharmaceutical

Origin	Activity of organism extracts against tumours first reported in 1969 (Cuevas and Francesch, 2008). Activity confirmed in 1983 but compound responsible not identified (Sigel et al., 1983).
Collection details	AHCE 1978 Collection Expedition on the R/V Alpha Helix. Visited Panama, Colombia, Nicaragua, Honduras, Belize and Mexico. Map of collection sites provided in Rinehart et al. (1981).
Purpose of collection	Marine bioprospecting for compounds with antibacterial, antiviral and cytotoxic activity (Rinehart et al., 1981).
Port of departure/ return	Panama
Vessel owner	US National Science Foundation
Research funders	Initial research funded by US National Science Foundation; National Institute of Allergy and Infectious Diseases; National Institute of General Medical Sciences; National Institutes of Health and the Proctor & Gamble Company.
Sample identification	The ascidian (seasquirt) *Ecteinascidia turbinata* - distributed throughout the Caribbean and in the temperate regions of the Atlantic and the Mediterranean
Location and date of duplicate sample deposit	Sample numbers provided in Rinehart et al. (1981) but species not yet identified fully at the stage of identifying activity.
Location and date of initial basic research	University of Illinois, Urbana Champaign Structure published in 1990 (Rinehart et al., 1990). Research on this organism began in 1981. Initial structures included in a PhD thesis in the mid-1980s. Also published by Harbor Branch Oceanographic Institution in 1990 (Wright et al., 1990). New mechanism of activity identified at US National Cancer Institute (Cuevas and Francesch, 2008).
Commercial interest	The Upjohn company of Kalamazoo Michigan, a pharmaceutical company, was involved in the original research. PharmaMar licensed compound from University of Illinois in the early 1990s.
Examples of patents associated	Initial filings: U.S. Patent Application Serial No. 872 189, June 9,1986; PCT Int. Appl. W08707610, 17 December 1987. Semi-synthetic process used for commercial production: PCT Int. Appl., 2000, WO 69862; PCT Int. Appl., 2001, WO 87895.
Compound production for trials and clinical use	Mariculture and on-land aquaculture used for initial Phase I and Phase II clinical trial supply from 1997 (Caribbean/W. Mediterranean & N. Africa). Compound present at 0.5–4.0 ppm. Total synthesis achieved in 1996. Semi-synthetic process developed by PharmaMar SA (Spain) (Cuevas and Francesch, 2008). Process involved modification of cyanosaframycin A (obtained from a marine-sourced bacterium).
Clinical approvals	Clinical trials carried out against soft tissue sarcoma. EU approval (EMA) for this indication in 2007. US FDA approval in 2015.
Final commercial product	Trabectidin, marketed as Yondelis by PharmaMar SA (Spain).

Halaven – marine sponge-derived pharmaceutical

Origin	Sponge extracts showed in vivo antitumour activity in early 1980s. Fujisawa Pharmaceutical Co. Ltd. carried out original bioactivity testing (Hirata and Uemura, 1986).
Collection details	The coast of Aburatsubo in the Miura Peninsula, which is to the south of Tokyo – 600 kg collected.
Purpose of collection	Bioprospecting
Port of departure/return	Not published
Vessel owner	Not published
Research funders	Foundation for the Promotion of Research on Medical Resources and Ministry of Education, Japanese Government. US National Cancer Institute for work carried in in New Zealand and initial clinical trials.
Sample identification	The sponge *Halichondria okadai*, *a* common, widely distributed sponge from the Pacific coast of Japan.
Location and date of duplicate sample deposit	Not stated
Location and date of initial basic research	Meijo University, Nagoya, Japan; Shizuoka University, Shizuoka, Japan.
Commercial interest	Fujisawa Pharmaceutical Co. Ltd. acknowledged in original publication. Some spectroscopic data obtained at Ono Pharmaceutical Co. Ltd. Eisai Ltd developed analogues via synthesis.
Examples of patents associated	Japanese patent JPH041751B2 1985 (Fujisawa Pharmaceutical Co). Derivatives US patent US5786492A (PharmaMar, SA, Spain). Synthetic halichondrin B 1994 (Harvard University, US). Eribulin patent family 1998 US Patent US8968298P (Eisai Co. Ltd. Japan). Most recent patent (RE46965) expires 2027.
Compound production for trials and clinical use	Total synthesis achieved in 1992 (Aicher et al., 1992). Analogue synthesis by Eisai (1998) needed pure halichondrin B for comparison (Yu et al., 2013). Halichondrin B for this study was obtained by wild, ecologically sustainable, collections of the New Zealand sponge *Lissodendoryx* sp. The Eisai synthetic work led to identification of analogue E7389/Eribulin, which was taken into clinical trials.
Clinical approvals	Halaven approved by US FDA in 2010 for treatment of metastatic breast cancer. EU EMA approval 2011.
Final commercial product	Eribulin, marketed as Halaven by Eisai Co. Ltd. (Japan)

The Commonwealth Blue Charter

Case Study

Marine Genetic Resources

Traceability of MGR in Fiji

"Our Blue Pacific has some of the world's highest marine biodiversity, which is yet to be fully discovered. We need to be part of the journey of discovery, and this requires genuine partnerships that include capacity development at their core, as well as equitable access to knowledge and the transfer of technology that can ensure our full participation into the future."

Bioprospecting Scientist, Fiji

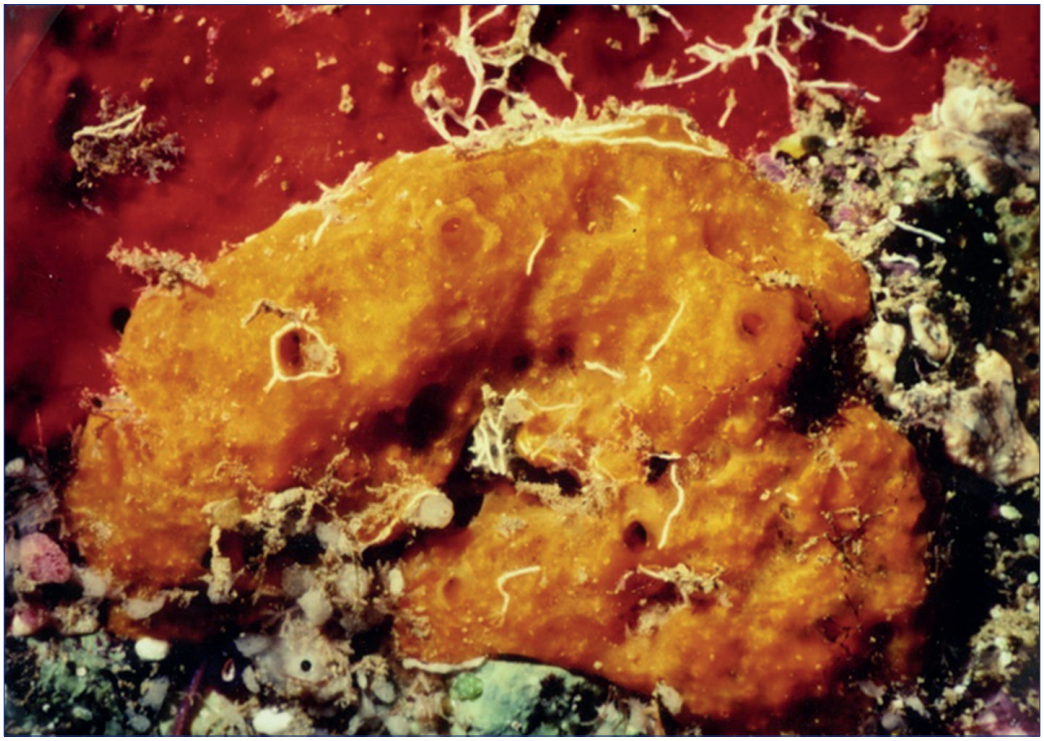


Figure 1. The sponge Jaspis cf. coriacea from Beqa Lagoon, Viti Levu, Fiji. Credit: Professor Phil Crews, University of California, Santa Cruz, US.

Summary

Like all small island states, Fiji's economic, environmental, social and cultural wealth is strongly connected to the biological diversity located in its ocean space, which is more than 70 times the size of its land area. Fiji has abundant coral reef ecosystems, which have been explored for the potential of their invertebrates to produce chemical compounds that may be of interest as potential pharmaceuticals. This case study examines the measures that Fiji has put in place to achieve traceability of its marine genetic resources (MGR) from initial discovery of biologically active compounds through to their development and eventual commercialisation for clinical application.

Issue

Marine bioprospecting in Fiji by international researchers started in the late 1970s and early 1980s, and resulted in several invertebrate-derived compounds and their analogues entering clinical trials. As an example, the sponge *Jaspis cf. coriacea* from Beqa Lagoon was found in 1986 to contain the bengamides, which showed early promise against cancer cells (Figure 1). Re-collection of the sponge led to preclinical trials in the mid-1990s (White et al., 2017). This was followed by the chemical synthesis of analogues, which entered human clinical trials for cancer in 2000 (Novartis) but were withdrawn in 2002 owing to side-effects. Subsequently, a great deal of work has been done on this compound family with a

range of potential other pharmaceutical applications. The bengamides were later discovered also to be produced by bacteria found outside of Fiji, showing that compounds are not always unique to one location. This has potential implications for benefit-sharing.

Tracing the above discovery from the reef to application is possible through scientific publications listing collection locations and timelines of discoveries, as well as interaction with the pharmaceutical industry (White et al., 2017). However, this level of traceability is not always achievable, especially during the subsequent product development stages carried out by industry.

The work described above began prior to the Convention of Biological Diversity (CBD; adopted 1992, in force 1993) and the supplementary 2010 Nagoya Protocol on Access and Benefit-sharing under the CBD. Under these new rules, any collection of MGR requires Prior Informed Consent (PIC) under Mutually Agreed Terms (MAT). The Nagoya Protocol also requires monitoring of the utilisation of MGR transparently through the use of checkpoints and internationally recognised certificates of compliance. Fiji, like other countries, had implemented an *ad hoc* permit system prior to the CBD. It is currently looking at updating and formalising its existing procedures.

Response

Fiji ratified the CBD in 1993 and acceded to the Nagoya Protocol in 2014. An extensive Global Environment Facility-funded study on access and benefit sharing for the Fiji Ministry of the Environment (the Ministry of Itaukei Affairs, which deals with policies and programmes relating to indigenous matters, was a stakeholder) in 2015. This study set out to formalise the procedures required under the Nagoya Protocol to ensure equitable benefit-sharing. Draft policies were developed but these were not fully operationalised. However, the system now requires certification from the CBD National Focal Point to show collectors have been through a consent process that is compliant with the Nagoya Protocol, but currently there is no central registry of consents given. Recent testing of Fijian MGR extracts against SARS-CoV2, the virus that causes COVID-19, demonstrated the potential value of these extracts and has reawakened government interest in developing Nagoya-compliant procedures.

The current system relies on good personal relationships between the Fijian researchers and their international collaborators, at the same time as close working with government officials. The steps to obtain consent to collect and export materials are as follows:

1. Research relationships are initiated through the preparation of a collaborative research agreement that sets out the essential expectations of the collaboration and aspects, such as collection of MGR, training of Fijian researchers, reporting and publication, among other aspects. In one case, when a company applied to carry out bioprospecting, it collaborated with the University of the South Pacific (USP).
2. Once the collaborative research agreement is established, a memorandum of understanding is signed by the international partner(s), the Fijian Ministry of Fisheries and Forestry and the Provincial Administration.
3. Collection is preceded by the obtaining of consent for qoli-qoli (traditional fishing rights) through negotiation with village elders and may involve a sevusevu (gift-giving ceremony). This process involves an explanation by the researchers as to what will be done with the materials collected and there is an expectation for periodic reporting-back, often via the Fijian research partners.
4. Once collected, samples are logged, and voucher specimens are kept at the marine collection at the USP, Suva campus.
5. Once the previous step is complete, permission to export MGR can be applied for at the Fijian Ministry of Fisheries and Forestry.

Traceability of MGR is achieved through annual reporting by the international partners of the work done with the Fijian MGR. These reports are collated by the Fijian partner and fed back to the Ministry of Fisheries and Forestry and Provincial Administrations, which should in turn forward information to the qoli-qoli owners.

Partnership and support

The majority of work on MGR is carried out at the Pacific Natural Products Research Centre (PNPRC), part of the Institute of Applied Sciences at USP. The PNPRC is well equipped to carry out the early stages of the bioprospecting process: collection; taxonomic identification; generation of extracts and fractions; and some biological assays. Given the complexity involved in identifying marine invertebrates, good relationships have been formed by the PNPRC scientists and for instance the Queensland Museum and Darwin Museum in Australia to enable accurate taxonomic descriptions of new species. Young Fijian researchers, mainly MSc students, at the PNPRC have been trained in relevant methods and, in many cases, have been provided with data to analyse and given guidance by the international collaborators. Several of these young researchers have obtained PhDs and further research experience outside of Fiji. International partnerships have thus provided some essential infrastructure for MGR bioprospecting, have trained young researchers and have included Fijian

Figure 2. Researchers from the PNPRC, Institute of Applied Sciences, USP, working with researchers from the Scripps Institution of Oceanography, University of California, San Diego, US. Credit: Institute of Applied Sciences, USP.

research teams on scientific publications. As a matter of respect, some publications acknowledge the Ratu (chief) who gave access to the qoli-qoli (Tabudravu, 2001).

Results, accomplishments and outcomes

The current system to obtain PIC/MAT in Fiji has to date worked well owing to the highly personal nature of the interactions. Relevant permits are facilitated by the Fiji partners and communication with international partners is good. Given that the overall number of international collaborations is low, the number of samples that are processed is manageable and can be manually curated in spreadsheets and the Bioprospecting Samples Database.

The investigation of Fijian reef invertebrates for potential pharmaceuticals has greatly increased knowledge on their taxonomic diversity. A taxonomic marine collection has been established at USP with a Bioprospecting Samples Database[1] that contains information on Fijian marine species, including taxonomic information, images and collection sites, with additional information (bioassay data, other scientific results) available on request. The collection contains voucher specimens of marine invertebrates and the international partner is expected to retain duplicates of these in their own collections. DNA samples are also taken and stored to augment taxonomic identification, although this is challenging for sponges as pure DNA is difficult to obtain. In-house identifiers are used but the key specimen identifiers used in the collection are mostly those assigned to specimens by the international partner. If additional identifiers are assigned to specimens, extracts, fractions and pure compounds, the PNPRC is to be provided with this information to allow tracking of results through the process, as shown in the annual reports. Within the PNPRC, facilities exist to carry out antimicrobial bioassays but other assays are performed outside of Fiji and results reported back and archived in the Bioprospecting Samples Database. Consolidation of data in this way is important in maintaining traceability and is possible within this database as there are relatively few entries and it is well curated.

The only example of a commercial transaction to date is the ongoing sale of a sponge-derived compound (jasplakinolide) used in biomedical research to a specialist chemical supplier. This brings in only limited income as the compound is not sold in large quantities. Some promising recently reported bioactives have been followed up for their biomedical potential, resulting in a few patents. However, in one of these cases (Fijimycins from a bacterium), a database search revealed them to be already known compounds; in another, a potential antimalarial (Bromophycolide from a red alga) was patented[2] but not much has been reported on its progress since 2013.

Challenges

One of the key challenges facing Fiji lies in implementing relevant Access and Benefit Sharing (ABS) legislation. The GEF ABS project seems to have moved some way towards the development of the relevant procedures but these still need to be completed and implemented. The government is yet to record the relevant procedures

1 https://ias.usp.ac.fj/bsdb/
2 US2011190338A1 Compounds and Compositions Useful in the Treatment of Malaria.

and processes on the ABS Clearing-House and there is no central database of PIC/MAT available to date. The current informal nature of the system is susceptible to significant disruption if there is staff turnover or if staff retire. Loss of funding to the PNPRC will also significantly affect the way the system works currently.

Traceability is manageable through annual reporting to the Fijian partners, although some partners file null reports in some years. The database system is small and some of the data is kept in separate spreadsheets. Integration of this data and expansion of the database will be needed if bioprospecting grows significantly in the future.

In terms of the science challenges, international collaborative funding has enabled the installation of more sophisticated facilities but some of these, such as liquid chromatography-mass spectrometry, have proved hard to maintain in a small island setting. Thus, ongoing international partnership and support is essential to maintain and develop the in-country marine bioprospecting programme. Of particular importance are taxonomic skills to identify marine invertebrates, preserve them and curate them in collection while maintaining an accurate database recording specimens and associated data.

Key lessons learnt

Good practice to date has meant that Fijian researchers are included in the research from the start and that training, equipment and opportunities to analyse data obtained at international collaborating labs are provided. This requirement to include local researchers in the research programme may be formalised soon and may mean a permit is needed from the Fijian Ministry of Education.

The approach used by Fiji, of starting small and growing procedures incrementally as required, has been successful. Additional funding alongside institutional support, including at government level, would be needed to effect a step-change, perhaps via encouraging an increase in the number of funded equitable international partnerships and perhaps allowing extension of the Bioprospecting Samples Database to include samples from other Pacific Island states.

Sources

The information in the case study was obtained from interviews with a variety of scientists and policy-makers in accordance with ethics approval from the University of Aberdeen

Jaspars, M., Rabone, M. and Humphries F., Tracing Options for Marine Genetic Resources (MGR) from Within National Jurisdictions. Report prepared for Commonwealth Secretariat, UK, June, 2021

Tabudravu, J., Morris, L. A., Kettenes-van den Bosch and Jaspars, M. (2001), Wainunuamide, a histidine-containing proline-rich cyclic heptapeptide isolated from the Fijian marine sponge Stylotella aurantium., Tetrahedron Letters, 42, 9273-9276

White, K. N., Tenney, K. and Crews, P. The Bengamides: A Mini-Review of Natural Sources, Analogues, Biological Properties, Biosynthetic Origins, and Future Prospects, (2017), J. Nat. Prod. 80, 740-755

The Commonwealth Blue Charter

For more information on these items, please contact us at bluecharter@commonwealth.int

Commonwealth Secretariat
Marlborough House, Pall Mall, London SW1Y 5HX, United Kingdom
Tel: **+44 (0)20 7747 6500**
www.thecommonwealth.org

D17584

The Commonwealth Blue Charter

Case Study

Marine Genetic Resources

Traceability of MGR in South Africa

"I discovered early on in my academic career (2011; in the field of marine microbial genomics) that the international scientific community is somewhat reluctant to collaborate with South African researchers owing to the government's bioprotection legislation. While such legislation is entirely within the spirit of the Convention on Biological Diversity, it is not always well aligned with standard scientific research practices, especially with respect to microbial and genomic resources, and therefore its practical implementation results in several complications that typically delay research programmes. The legislation is geared more towards the protection of the macrobiology (flora and fauna); however, this is evolving. Especially with the take up of 'omics' technologies, the research community has grown and has a voice to inform on the broader effort to support the conservation and sustainable use of marine genetic resources."

Bioprospecting Scientist, South Africa.

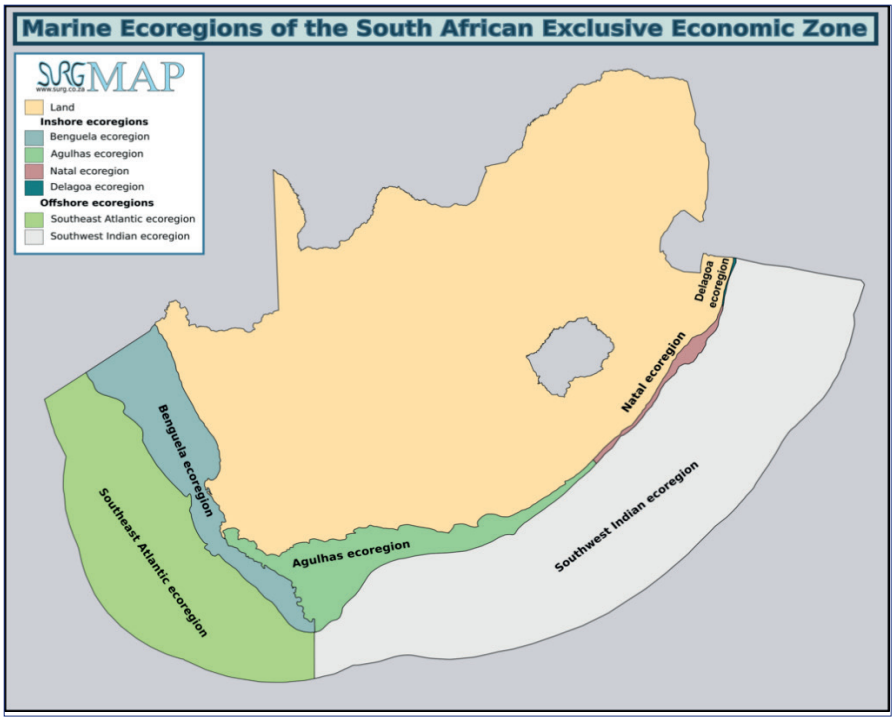


Figure 1. Marine eco-regions of the South African Exclusive Economic Zone. Source: Peter Southwood, CC BY-SA 4.0.1

Summary

This case study discusses the South African systems put in place to trace marine genetic resources (MGR) from collection through research to development and eventual commercialisation. It highlights the procedures to enable access to South African MGR and subsequent benefit-sharing though a system of prior informed consent (PIC) under mutually agreed terms (MAT).[2] The South African system is based on the National Environmental Management: Biodiversity Act of 2004 (updated 2015) and its 2008 Bioprospecting Access and Benefit-Sharing Regulations, which are the

1 https://commons.wikimedia.org/w/index.php?curid=71484741

2 This is one of several possible approaches, as discussed in [reference main report].

main regulatory instrument.[3] These cover "the fair and equitable sharing of benefits arising from bioprospecting involving indigenous biological resources." The Act and its 2015 revision meet the requirements of the Convention on Biological Diversity (CBD) and the Nagoya Protocol, to which South Africa became a party in 2014, and require any collections of indigenous biological resources to be made with PIC and under MAT, to ensure any benefits are equitably shared. South Africa's marine ecosystems are extremely diverse and can be divided into several zones – into Atlantic and Indian zones further off-shore and four defined near-shore regions. Levels of endemism in the marine environment (i.e. species occurring only in South African waters) are reported to include up to one-third of all South African species described to date, increasing chances of successful marine bioprospecting research (Figure 1; Sink et al., 2019).

Issue

Traceability of information on research and development on MGR in South Africa is possible in a couple of cases, via the scientific literature, but the subsequent development of compounds in pharmaceutical companies is challenging to trace. This is because there is no clear way to discover it in the patent literature, owing to structures and associated compound names or codes changing. Traceability becomes much more challenging once a compound reaches the phase of commercial development.

Terrestrial bioprospecting in South Africa is well established, often using traditional and indigenous knowledge, but marine bioprospecting is less developed and active in only a few research groups, mainly based at universities. One example is work carried out by international researchers that showed that South African marine invertebrates produced very promising compounds (Bolton, 2013). One of the most potent compounds ever discovered worldwide, cephalostatin, obtained from the southern Cape tube worm *Cephalodiscus gilchristi* by a US group in 1988, showed early promise but the quantities needed for further studies could not be obtained from collection of the organism, or easily made via chemical synthesis (Pettit, 1988). Nevertheless, its unique mode of action is still of interest to cancer biologists and for this reason attempts to chemically synthesise it continue to this day (Rudy, 2008).

Another South African example, the Sodwana Bay sponge *Hemiasterella minor*, was discovered in 1994 to produce hemiasterlin, which killed cancer cells at low concentrations (Talpir, 1994). Subsequently, this compound was rediscovered by a Canadian group from a Papua New Guinea sponge, and was used as the inspiration for a synthetic analogue E7947, which has been in clinical trials for hepatic, prostate and bladder cancers (Kuznetsov, 2009). Analogue synthesis was carried out by a Japanese pharmaceutical company and subsequently these have been used as "warheads" directed to cancer tumours by antibodies (Newman, 2021).

The above collections were made prior to South Africa's ratification of the CBD (1996) and the Nagoya Protocol (2014), meaning that, if benefits eventuate from commercialisation of these compounds, a share of these may not be returned to South Africa. In addition, in the second case, there is no direct link between the initial discovery in South Africa and further development based on the same material discovered from a Papua New Guinea sponge.

Response

In South Africa, the necessary infrastructure and procedures to enable access and the equitable sharing of benefits resulting from bioprospecting were created as part of the country's 2004 National Environmental Management: Biodiversity Act of 2004 (updated 2015) and its 2008 Bioprospecting Access and Benefit-Sharing Regulations.[4] The material scope of the Act is broad and includes indigenous biological and genetic resources, meaning species, their genes and biochemical compounds. The Act also covers collections used for bioprospecting. The Act includes bioprospecting for commercial applications but also biotrade where biological resources are used for the production of other products such as medicines and essential oils. Research utilisation of indigenous biological and genetic resources is also covered. The Act divides the process into discovery and commercialisation phases and separate procedures exist for each. Information on the requirements of the Act can be found on the Access and Benefit-Sharing Clearing House of the Republic of South Africa website,[5] which also contains links to the necessary forms to be completed and returned to the Department of Environment, Forestry and Fisheries to obtain a permit.[6] For research other than bioprospecting, such as basic marine scientific research, bioprospecting permits are not needed unless material is exported, in which case a permit is required, even for basic research. Marine

3 https://www.environment.gov.za/sites/default/files/legislations/bioprospecting_regulatory_framework_guideline.pdf

4 Ensuing from the Act, Bioprospecting, Access and Benefit-Sharing Regulations were developed in 2008 and amended in 2015, and are now administered by the Department of Environment, Forestry and Fisheries, which simultaneously acts as National Focal Point and National Competent Authority for the CBD and Nagoya Protocol (Silvestri et al., 2020).

5 https://www.environment.gov.za/projectsprogrammes/bioprospectingaccess_benefitsharing_babs_clearinghouse

6 https://www.environment.gov.za/projectsprogrammes/bioprospectingaccess_benefitsharing_babs_clearinghouse#application_forms

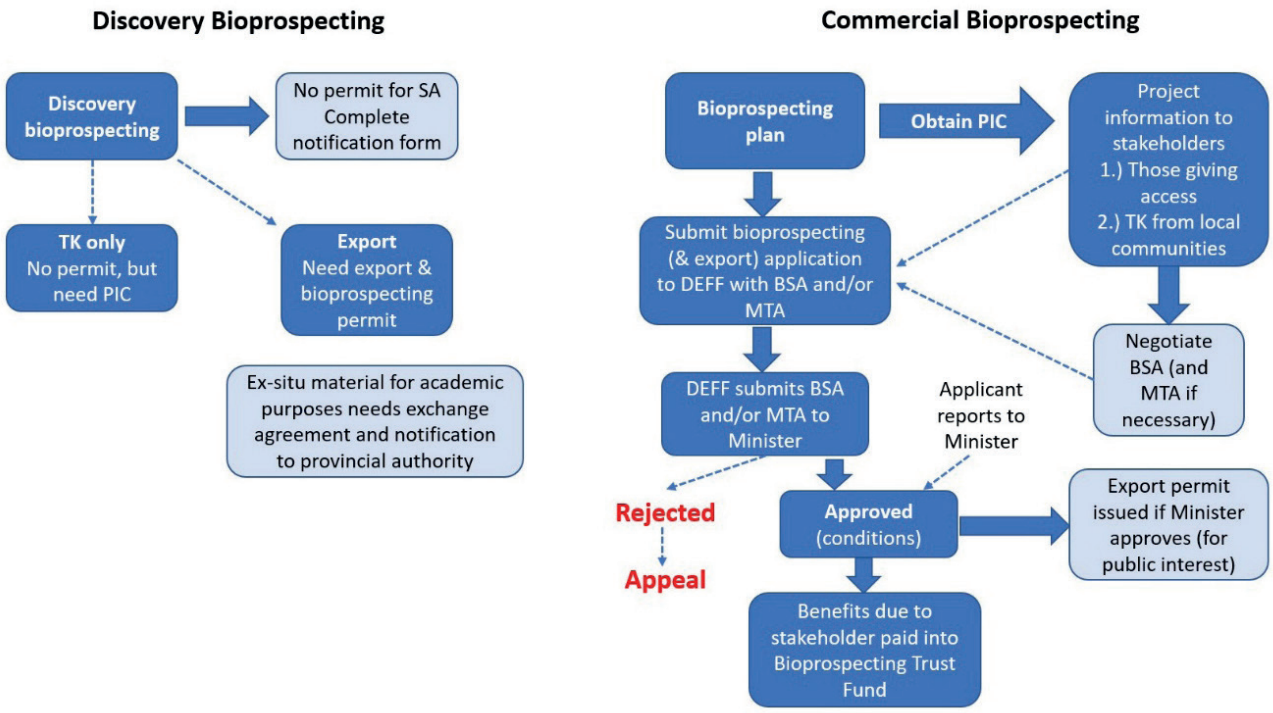


Figure 2. Steps that need to be taken to ensure legal certainty over South African indigenous biological resources for discovery or commercial bioprospecting and export

biological resources are covered by the Marine Living Resources Act, and a research permit from the relevant branch of the Department of Environment, Forestry and Fisheries should be obtained before collection.

The current system requires the following steps to be taken to obtain PIC/MAT and, if needed, permission to export, indigenous biological and genetic resources for research purposes or utilisation in bioprospecting (Figure 2):

1. A Bioprospecting Discovery Phase Notification for basic research is made before the research starts. The application form gathers details on applicants and the project objectives as well as on indigenous biological resources to be collected.

2. Permission to export indigenous biological resources can be applied for as part of the bioprospecting discovery phase and should be accompanied by a Material Transfer Agreement and a Benefit-Sharing Agreement where relevant.

3. The bioprospecting discovery phase requires an annual status report, to cover biological resources collected, research conducted, progress towards commercialisation, patent applications, engagement with industry, patent licensing, transfer of materials and any revenues generated.

4. The commercialisation phase of bioprospecting starts with a Bioprospecting Permit Application. The application requires a longer project proposal and the identification of all stakeholders to give access to indigenous biological and genetic resources. However, MGR are a "national competence," so this permission comes from the government itself. International researchers must apply for this permit jointly with a South African institution or researchers.

5. Export permission can also be applied for as part of an Integrated Export and Bioprospecting Permit and must include a Material Transfer Agreement and a Benefit-Sharing Agreement.

Traceability of downstream uses of South African indigenous biological and genetic resources is captured in the annual status update form that must be returned to the Department of Environment, Forestry and Fisheries and that must include reporting of certain events, including patenting, commercial use and clinical trials, but scientific publication is not included. Annual status reports are often sent via the technology transfer office of the institution carrying out the bioprospecting research. which will forward the final report to the Department of Environment, Forestry and Fisheries.

During the scientific part of the process (the "bioprospecting discovery phase"), good scientific practice ensures that any compounds with properties of interest can be traced back to the original MGR. Work on invertebrates and marine microorganisms in universities usually uses local identifiers for materials and data derived from MGR used in bioprospecting. Associated information is maintained in local databases or spreadsheets, where all information is collated, such as taxonomic identification, links to DNA sequences, biological assay data and biochemical compounds obtained. The Biodiversity Act does not require this level of tracking of materials through the process but

scientifically it is justified to enable accurate identification of materials of interest for further investigation.

Partnership and support

Although there is capacity to carry out all stages of the discovery phase of the bioprospecting process, South African researchers benefit from being part of large international consortia such as the EU Project PharmaSea[7] (2012–2017), which included researchers from the Institute for Microbial Biotechnology and Metagenomics at the University of the Western Cape, and a research agreement allowed other partners in this consortium to investigate materials. Being included as equal partners within international consortia complements, and in some cases can significantly expand, existing research capacity, creates networks and enables staff and student exchanges for skills and knowledge exchange and training, while also enabling access to scientific capacity and expertise that is not available in South Africa.

Results, accomplishments and outcomes

The South African National Biodiversity Assessment shows the high degree of endemism of South African marine species, which points to their potential value for bioprospecting (Sink et al., 2019). To date, the Department of Environment, Forestry and Fisheries has issued 105 bioprospecting permits, many of which are integrated export and bioprospecting permits (14) or include biotrade and bioprospecting (27).[8]

The question as to whether digital sequence information (DSI) should be covered by the Biodiversity Act and subject to benefit-sharing provisions is under active discussion within the South African government.

At the current time, marine invertebrate specimens are stored at the South African Institute for Aquatic Biodiversity Collections[9] and the database is searchable via the Global Biodiversity Information Facility (GBIF).[10] A positive outcome of the Biodiversity Act for traceability is an initiative to establish a national biobank and database. This will increase understanding of marine biodiversity and improve efforts to conserve it by providing baseline data. The South African National Biodiversity Institute has such a database for indigenous plant species, and the South African Department of Science and Innovation has just approved a National Biobanks initiative, which will provide for core biobanks for non-plant collections, among others microbial collections, and a nationally and internationally accessible database to the biobank.

Challenges

The steps to obtain PIC/MAT and undertake bioprospecting or even basic research represent a significant bureaucratic burden. The lengthy annual status update forms require a large amount of information, which may not be available until much later in the bioprospecting process. Approval timeframes can be long, with up to 120 days needed to obtain an export permit. For the bioprospecting discovery phase in universities, this administration is carried out by researchers and technology transfer offices. The effect of the Act and related regulations with the associated administrative burden therefore appears to have had something of an unintended dampening effect on bioprospecting efforts and research activities generally in South Africa (see opening quotation).

MGR or derivatives will likely be exported outside of South Africa for multiple reasons – for example so a service provider can perform tests on the biochemical compounds that are not readily available in South Africa. Such out-of-country work requires an export permit, which entails an arduous and lengthy process, even though the service provider does not need to know the identity of the material and should have no rights over the material.

Despite implementation of the regulations, challenges and gaps in traceability remain evident. In particular, the commercial phase in the supply and value chain would benefit from greater transparency.[11] Additionally, not requiring citation of the relevant Biodiversity Act permit in academic publications reduces the opportunity for increased traceability via this route. The link between the South African Institute for Aquatic Biodiversity Collections and GBIF is currently maintained by volunteers; continuing in the longer term on this basis will be challenging.

Key lessons learnt

The system put in place by the Biodiversity Act has divided the discovery and commercial phases of bioprospecting and created separate processes for each. South African researchers sense that the international research community is reluctant to collaborate with them because of the onerous procedures involved in obtaining PIC and MAT and the lengthy period before an export permit can be obtained. Nevertheless, the diversity of

7 http://www.pharma-sea.eu/

8 The document does not indicate the start date of data collection – only the end date (21 May 2020): https://www.environment.gov.za/sites/default/files/docs/bioprospectingpermits_issued21may2020.pdf

9 https://www.saiab.ac.za/saiab-collection-facility.htm

10 https://www.gbif.org/dataset/1aaec653-c71c-4695-9b6e-0e26214dd817

11 See Section 1.2 in the main report.

South African biological resources means that South African researchers are often integrated in international bioprospecting projects.

The move towards improving national collections/ biobank facilities is important for both future conservation efforts and successful bioprospecting campaigns, and avoids duplication of effort. Well-documented collections are critical to expanding research capacity as the majority of biological research, including initial bioprospecting, is specimen-based. Linking these collections' databases to global networks such as GBIF would mean that data on South African marine bioresources is searchable and accessible globally and encourage international collaboration.

Sources

The information in the case study was obtained from interviews with a variety of scientists and policy-makers in accordance with ethics approval from the University of Aberdeen

Bolton, J. J., Davies-Coleman M. T. and Coyne, V. E. (2013) Innovative processes and products involving marine organisms in South Africa, African Journal of Marine Science, 35, 449-464

Kuznetsov, G., TenDyke, K., Towle, M. J., Cheng, H. et al, (2009) Tubulin-based antimitotic mechanism of E7974, a novel analogue of the marine sponge natural product hemiasterlin. Molecular Cancer Therapeutics, 8, 2852

Newman, D. J., (2021) Natural Product Based Antibody Drug Conjugates: Clinical Status as of November 9, 2020. J. Nat. Prod., 84, 917-931.

Pettit, G. R., Inoue, M., Kamano, Y., Herald, D. L. et al (1988), Isolation and structure of a powerful cell growth inhibitor cephalostatin 1, J. Amer. Chem. Soc. 110, 2006-2007

Rudy, A., López-Antón, N., Dirsch, V.M., and Vollmar, A. M. (2008), The cephalostatin way of apoptosis, J. Nat. Prod. 71, 482-486

Sink, Kerry, J; Van der Bank, Megan; Majiedt, Prideel; Harris, Linda; Atkinson, Lara; Kirkman, Stephen; Karenyi, Natasha (29 September 2019). South African National Biodiversity Assessment 2018 Technical Report (Report). 4: Marine Realm. South African National Biodiversity Institute. http://opus.sanbi.org/jspui/handle/20.500.12143/6372

Silvestri, L., Sosa, A., McKay, F., Diniz Vitorino, M., et al. (2020) Implementation of access and benefit-sharing measures has consequences for classical biological control of weeds. BioControl, 65, 125-141.

Talpir, R., Benayahu, Y., Kashman, Y., Pannell, L., and Schleyer, M., (1994) Hemiasterlin and geodiamolide TA; Two new cytotoxic peptides from the marine sponge Hemiasterella minor (Kirkpatrick), Tetrahedron Letters, 35, 4453-4456

The Commonwealth Blue Charter

D17585

For more information on these items, please contact us at bluecharter@commonwealth.int

Commonwealth Secretariat
Marlborough House, Pall Mall, London SW1Y 5HX, United Kingdom
Tel: **+44 (0)20 7747 6500**
www.thecommonwealth.org

Endnotes

1 Including the Food and Agriculture Organization International Treaty for Plant Genetic Resources for Food and Agriculture (ITPGRFA) and the World Health Organization Pandemic Influenza Preparedness Framework.

2 https://www.cbd.int/dsi-gr/

3 See Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources (2020a; 2020b).

4 Countries are negotiating an international legally binding instrument under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of the marine biological diversity of areas beyond national jurisdiction, which is likely to have a definition of marine genetic resources (https://www.un.org/bbnj/).

5 Derivatives are referenced in the Nagoya Protocol only in Article 2, and some jurisdictions take a nuanced view (e.g. see the Section 2.3.4, p. 16, of EU, 2021).

6 https://www.marinepharmacology.org/

7 For example on internationally recognised clinical trials databases such as https://www.isrctn.com/ and https://clinicaltrials.gov/.

8 https://www.marinepharmacology.org/

9 https://pubs.rsc.org/marinlit/

10 http://www.nautilusbiosciences.com/en-gb/

11 https://pharmamar.com/

12 https://www.griffith.edu.au/institute-drug-discovery/unique-resources/naturebank

13 https://www.aosis.org/reports/international-framework-for-laws-governing-deep-sea-depends-on-the-technological-readiness-of-small-island-states/

14 Adapted from United Nations General Assembly (2019).

15 http://www.pharma-sea.eu

16 In the deep-sea, most species remain undescribed, therefore most biodiversity in deep-sea environments remains unknown to science. These knowledge gaps on deep-sea taxonomy are compounded by the fact that the science field of taxonomy - the study and description of new species - is a very time-consuming process and describing new species can take several years (Glover et al., 2018).

17 Bulk preserved samples, also known as "specimen lots," – that is, all specimens from a given sampling event – are preserved and stored in their entirety for later identification, sometimes on a long-term basis. Other batch or bulk samples are "environmental samples," intended for environmental DNA (eDNA) analysis. For example, a sediment sample is preserved in bulk, and may be later sorted to isolate individual specimens; an environmental sample may be processed and extracted for eDNA studies.

18 Regarding criteria for identifiers, "persistence" is assurance of availability of the identifier long term, resolvability that the identifier itself can be used to directly discover the data objects and discoverability that identifiers can be discovered/

exposed within and across systems; authority refers to curation and standardisation of the identifier, important so that they remain viable long term (see Guralnick et al., 2014, 2015 for further elaboration). Examples of persistent identifiers that meet such criteria include the well-known digital object identifiers (DOIs) for publications and global unique identifiers (GUIDS) for specimen records (see case study in Rabone et al., 2019).

19 As an example, records in London's Natural History Museum collections database EMu are published on the museums data portal (https://data.nhm.ac.uk/). Here, GUIDS are the persistent identifiers and embedded in the web link in the specimen record on the portal. Like many museum and university databases, EMu is harvested by the global biodiversity database GBIF (the Global Biodiversity Information Facility) (https://www.gbif.org/).

20 https://www.go-fair.org/fair-principles/. See also Wilkinson et al. (2016).

21 Some analysis will necessitate destructive sampling, whereby the entirety of the original sample is used and no subsampling is possible. This may be the case for tiny organisms or an eDNA sample (e.g. water samples).

22 The global bioinformatics infrastructure, which contains millions of DNA sequences.

23 Prior to publication, specimens in a museum, for example, will also be accessioned into the collections (voucher specimens) and allocated a registration/accession number, a locally unique identifier, often referenced in a publication. These voucher specimens provide a reference for future work on the given species.

24 For example https://www.gbif.org/dataset/f70aae50-d156-45d8-a0d1-645231732822

25 https://absch.cbd.int/

26 Regarding versioning, the ABSCH generates the unique identifier relevant to the IRCC (or any other information a country provides), which can link the IRCC to the country's original and more detailed collection permit. According to the ABSCH website (https://absch.cbd.int/), each record published in the ABSCH is assigned a distinct UID – a combination of characters and numbers used to uniquely distinguish the records on the ABSCH. This might look something like this: ABSCH-IRCC-MX-123456-1. Each time a record is updated, the last number of the UID, called the revision number, is increased by 1, indicating a new version. This makes it possible to track amendments to records and provides greater transparency. The UID can be a useful way to locate and keep track of records, as well as to link ABSCH records to information contained in a separate database. This can be helpful, for example, to make links between an IRCC and a national permit or its equivalent, which can contain additional and confidential information not available on the ABSCH.

27 The World Federation for Culture Collections has addressed the challenges for national authorities in updating IRCC by proposing an external resolution mechanism using the global catalogue of microorganisms (see Conference of the Parties to the CBD, 2014).

[28] For the SMTA under the ITPGRFA, see http://www.fao.org/plant-treaty/areas-of-work/the-multilateral-system/the-smta/en/. For one of the types of SMTAs concerning influenza genetic resource-sharing under the World Health Organization's Pandemic Influenza Preparedness Framework, seehttps://www.who.int/influenza/pip/virus_sharing/SMTA1_eng.pdf

[29] See, for example, the Micro B3 Agreement: https://www.microb3.eu/sites/default/files/pdf/MICRO_B3_ABS_model_agreement_17122013%20explanatory%20notes.pdf

[30] https://creativecommons.org/licenses/

[31] Conservation of Biological Diversity and Resources, Access to Genetic Resources and Benefit Sharing, Regulation 2006 (Kenya), Section 18.

[32] Law 13,123 of 20 May 2015, on Access and Benefits Sharing of Genetic Resources and Associated Traditional Knowledge.

[33] There is not yet agreement on a global minimum standard about the form and effect of the requirement. However, a study by the World Intellectual Property Organization (WIPO) noted that, as at 2020, there were more than 30 countries with disclosure of origin requirements (WIPO, 2020 p. 8). The WIPO study discusses a variety of country approaches and identifies key questions for policy-makers when considering the opportunities and challenges of implementing a disclosure of origin requirement.

[34] OBIS: https://obis.org; GBIF: https://www.gbif.org; WoRMS: http://marinespecies.org/

[35] http://www.insdc.org/

[36] https://www.ggbn.org/

[37] https://dtp.cancer.gov/organization/npb/open_repository.htm

[38] https://www.hi.no/en/hi/laboratories/tromso-department1

[39] https://www.griffith.edu.au/institute-drug-discovery/unique-resources/naturebank

[40] https://dtp.cancer.gov/organization/npb/docs/NCI_LOC_NPCA_Aug2015.pdf

[41] https://dtp.cancer.gov/organization/npb/docs/MTA_Active_and_Open_2-9-21.pdf

[42] Recording of locality data with sequences may not be relevant in some cases – for example for sequences isolated from model organisms/lab-strains.

[43] Examples of relevant initiatives/networks developing and linking collections include GGBN (https://www.ggbn.org/), the Consortium of European Taxonomic Facilities (https://www.cetaf.org), the Distributed System of Scientific Collections (https://www.dissco.eu/), SYNTHESYS (www.synthesys.info) and the Earth BioGenome Project (https://www.earthbiogenome.org). Databases relevant to networks of collections include GBIF, OBIS and the Taxonomic Databases Working Group. See Rabone et al. (2019) and Collins et al. (2020) for further information.

[44] Link to case study to be added

[45] Link to case study to be added.

46 https://www.environment.gov.za/sites/default/files/legislations/bioprospecting_regulatory_framework_guideline.pdf

47 https://www.environment.gov.za/projectsprogrammes/bioprospectingaccess_benefitsharing_babs_clearinghouse

48 The potential impact of any traceability system on non-commercial applications and basic research must be considered. It is therefore helpful to compare potential research impacts, practicalities and costs for governments for each traceability option.

49 https://abs-sustainabledevelopment.net/story/a-pilot-to-improve-genetic-resources-traceability-through-blockchain-technology-by-the-undp-gef-global-abs-project/

50 https://fishcoin.co/#seafood-industry

51 https://www.earthbankofcodes.org

Commonwealth Secretariat
Marlborough House, Pall Mall
London SW1Y 5HX
United Kingdom

thecommonwealth.org

The Commonwealth

D17583