Genetic Testing in Natural History Studies: A Review of the Regulatory and Legal Landscape

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Abstract

Background: Natural history (NH) studies, using observational methods, are common in rare and orphan diseases (80% of which have a genetic component). There is profound interest in identifying genetic mutations driving these diseases in these studies to support the formulation of targeted precision medicines. The global regulatory classification of NH studies with novel molecular biomarker collection has not been clearly delineated, presenting researchers with the challenge of determining how these studies are classified and regulated across multiple geographies. **Objective:** The aim of this investigation was to conduct a review of regulations related to NH studies and genetic testing to elucidate regulatory pathways to inform clinical researchers in the field. **Methods:** Regulatory provisions for NH studies and genetic testing were obtained from Pharmaceutical Product Development (PPD)'s propriety regulatory intelligence database and by surveying the company's country-specific regulatory experts. A literature search was conducted in the

Google Scholar search engine and PubMed for supplementary information. **Results:** Nineteen countries were evaluated; 37% classified NH studies with biomarker collection as noninterventional and 26% required regulatory approval (increasing to 47% when molecular biomarker testing was introduced). No regulatory provisions for genetic testing could be identified in 32% of countries, and 58% did not have binding requirements for genetic counseling. **Conclusion:** Lack of harmonization of regulations governing NH studies with molecular biomarker collection contributes to the operational complexity of conducting multinational studies in orphan and rare diseases. A set of harmonized international guidelines for these studies would improve efficiency, and this may be on the horizon with the recent adaptation of International Conference on Harmonisation (ICH) guideline E18.

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Introduction

Since the 1983 enactment of the US Orphan Drug Act, many advancements in the development of pharmaceutical products for rare diseases have been made. Although

there is no singular definition for what constitutes a rare disease, the designation is given, in part, to diseases or subsets of common diseases affecting fewer than 200,000 people in the USA [1], less than 5 per 10,000 in the European Union (EU) [2], and fewer than 50,000 patients in Japan [3]. These rare pathologies, many of which are serious or life-threatening conditions [4], include genetic defects, autoimmune disorders, infectious diseases, neurological disorders, and certain types of cancers, among other types of illnesses [5].

To date, there are approximately 7,000 rare diseases, collectively affecting approximately 400 million people globally [6]. Provisions such as the EU Regulation 141/2000 on orphan medicines [7], which is equivalent to the US Orphan Drug Act, and the 21st Century Cures Act [8] in the USA have emerged over the years to help catalyze orphan drug development. The collaboration of patient advocacy groups with government officials and rare disease researchers has also played a role in ensuring access to safe treatment for patients. Yet, only 5% of rare diseases currently have an approved medicinal therapy [6]. With new rare diseases identified as a result of advancements in health technology and precision medicine, the development of new therapies is warranted.

Natural History Studies in Rare Diseases

Noninterventional (observational) real-world evidence studies complement traditional clinical trial data and are necessary for a successful market launch of, and patient access to, novel therapies. Noninterventional studies evaluate data “of ongoing medical care without ‘controlling’ the therapy beyond normal medical practice” [9]. Employing observational methods, natural history (NH) studies are defined as “studies that follow a group of people over time who have, or are at risk of developing, a specific medical condition or disease. A natural history study collects health information in order to understand how the medical condition or disease develops and how to treat it” [10]. Essentially, they are designed to quantify the incidence or prevalence of a disease and describe patient characteristics (e.g., demographic, genetic, and environmental), usual care treatment patterns (e.g., treatment modalities and unapproved treatment options), and the natural evolution of a disease [11]. NH data can be used to document unmet clinical needs and the burden of an illness; it can also populate synthetic control arm analyses and disease, health economic, and trial simulation models – methods and approaches that are becoming increasingly important for the value demonstration of advanced therapies.

The US Food and Drug Administration (FDA) released a draft guidance in 2019 underscoring the importance of NH studies in rare disease research: *Rare Diseases: Natural History Studies for Drug Development* [10]. Officially introducing real-world evidence in the development of orphan drugs, the guidance expands on the paucity of rare disease NH data, with the objective of guiding industry on the design and execution of these studies.

Genetic Testing in NH Studies

Understanding the genetic origins of a disease – such as genotype and the specific types of gene mutations – can be highly predictive of etiology, diagnosis, or severity and indicative of response to treatment. As such, it can lead to the identification of new genomic biomarkers defined by the International Conference on Harmonisation (ICH) (E15) as “A measurable DNA and/or RNA characteristic that is an indicator of normal biological processes, pathologic processes, and/or responses to therapeutic or other interventions [12]” or predictive tests. However, with an estimated 80% of rare diseases having a genetic component involving 1 or several genes [13], there is interest in identifying genetic mutations driving these diseases. Additionally, biomarker identification in rare diseases is integral for the development of novel treatments as tailored therapies can be formulated to treat the underlying genetic cause of a disease, thereby improving symptoms and potentially extending a patient’s life span [14]. Molecular biomarkers also have the potential to identify subgroups of patients suffering from more common diseases (e.g., genetic mutations linked to obesity) [15]. This has led to progress in rare disease drug development of small patient populations that previously had been difficult to treat. For instance, the poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor olaparib was approved by the US FDA in 2018 for the treatment of patients with a rare and lethal form of breast cancer caused by a breast cancer gene mutation previously treated with chemotherapy [16].

Regulatory Interpretation of Genetic Testing in NH Studies

The emergence of the *Rare Diseases: Natural History Studies for Drug Development* FDA guidance [10] introduces a new kind of study, where the collection or identification of a biomarker is considered integral to the understanding of the NH of rare diseases. A quandary exists; therefore, when genetic data are required for the study but have not already been collected as per usual care or

are simply unavailable. More specifically, mandated genetic testing in a rare disease NH study may shift the classification of the study from noninterventional to interventional or low intervention. Typically, interventional research evaluates the effects of experimental interventions (e.g., pharmacological, surgical, device, or diagnostic) that do not conform to routine practice. Exposure to an intervention in a clinical setting may pose a certain element of risk to participants. This interpretation of an interventional study broadly aligns with the definition of a clinical trial in EU legislation (Clinical Trials Directive 2001/20/EC [17] and Clinical Trials Regulation 536/2014 [18]) and the National Institute of Health (NIH) US Library of Medicine's definition of an interventional study [19]. This definition has been adopted by the majority of regulatory agencies in the EU, USA, and Canada. In the EU, the term "low intervention" has emerged from regulation 536/2014 and is applied to studies where an investigational medicinal product is tested within the terms of its marketing authorization, or its use is evidence-based and supported by published safety and efficacy data, and any additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice [18].

To our knowledge, the global regulatory classification and provisions of NH studies with genetic testing have not been clearly delineated in the literature, which presents researchers with the following challenge: how to determine how these studies are classified (noninterventional, interventional, or low intervention), legislated for, and regulated across multiple geographies? The goal of this investigation is to conduct a review of the regulatory provisions and literature to resolve this question on a country-by-country basis using international regulations related to introducing genetic testing in NH studies. In addition, the authors provide practical insights into the design and conduct of NH studies with a biomarker component, while also outlining considerations for patients. This brief and targeted review is of interest to researchers of multinational orphan and rare disease clinical research, and rare disease patient advocacy groups who partner with researchers and support patients.

Methods

Information regarding the national provisions for research involving biomarkers and genetic testing was obtained through Pharmaceutical Product Development, LLC (PPD)'s local regulatory intelligence system, RegView [20]. PPD RegView includes de-

tailed regulatory content and information from market-relevant geographic areas of research. The proprietary internal system is easily searchable, supports fast, reliable workflows for users, and is updated via a global network of PPD's in-country regulatory teams. The regulatory intelligence database includes a built-in process for updating, reviewing, and approving new content to ensure that information is up-to-date and that the most current laws, guidelines, and requirements are followed.

An initial search of PPD RegView was performed between April 14 and July 15, 2019, followed by a survey of in-country PPD regulatory experts to verify and supplement information stored in the system. Locally verified regulatory information was received for 19 countries in major geographic regions (Europe and Middle East: Belgium, Bulgaria, France, Germany, Israel, the Netherlands, Portugal, Spain, Switzerland, the UK, and Ukraine; Asia Pacific: Australia, Japan, and South Korea; North America: Canada and the USA; Latin America: Argentina, Brazil, and Mexico), which are reported here. The authors acknowledge that NH studies are performed in other important locations, including China and India; however, other countries were excluded due to the absence local data verification. This is a limitation that provides scope for future work. The searched areas of interest regarding NH study provisions with prospective biomarker collection encompassed the legislation, official laws, or legally binding guidelines for low-intervention studies; the regulatory determination of NH studies with novel prospective biomarker collection; and whether these studies are subject to ethics committee (EC) and/or regulatory authority approval. The authors defined NH studies with novel prospective biomarker collection as prospective studies whose purpose is to extend the knowledge of the natural course of a disease and its genetic determinants through the collection of genetic biomarkers. However, classification of these studies internationally is unclear and is subject to interpretation. Searches also focused on the legislation, official laws, or legally binding guidelines surrounding genetic testing and genetic counseling, and requirement for ECs and/or regulatory authority approval in the context of NH studies.

In addition, a literature search was conducted for the period 2012 to present in the Google Scholar search engine and PubMed, using the following Boolean search criteria <((intitle:"genetic testing" OR intitle:"genetic screening" OR intitle:"genetic counseling") AND ("law" OR "legal" OR "statutory" OR "statute"))> to obtain published material that served to provide supplementary details on country-specific legislature and healthcare frameworks. The period before 2012 was not searched to avoid gathering material that was obsolete or had been superseded due to the fluctuating genetic testing landscape and provisions for rare disease following the introduction of the Genetic Information Nondiscrimination Act (GINA) in the USA (2007), the Oviedo protocol on genetic testing for health purposes (2008), the German Genetic Diagnostics Act (2010), and Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border health care. The latter includes several notable provisions relating the diagnosis and management of rare disease in the EU [21]. The search returned 3,340 citations, of which 36 English language publications were retained. These searches were not performed as a formal systematic review, and therefore, there were no set inclusion/exclusion criteria for the selection. However, most citations were discarded due to the primary focus being on molecular genetics, clinical practice, or bioethics, rather than regulation or legislation. Finally, data gathered

Table 1. Summary of regulatory framework and provisions for NH studies with prospective biomarker collection

Country	LI trial defined in country regulation (+, yes; -, no)	Classification of NH studies with novel prospective biomarker collection	EC approval required (+, yes; -, no)	RA approval required (+, yes; -, no)	Comment
Argentina	–	NI	+	–	RA notification needed for import of sample materials
Australia	–	NI	+	–	
Belgium	–	NI/INT	+	–	The study is NI if collection of biomarkers adheres to routine practice, and INT if nonroutine tests are performed
Brazil	–	INT	+	–	EC approval only – local and central EC (CONEP). Central review applies to projects sponsored by foreign companies. RA notification needed for import of sample materials and of exports of samples
Bulgaria	–	NI	+	–	Regulation that will define LI studies and approval requirements is currently being considered.
Canada	–	NI	+	–	
France	+	LI/NI	+	+	LI studies involve only minimal risks and constraints and may only involve health products for approved for use NH studies with prospective novel biomarker collections may be classified as LI or NI, depending on order dated April 12, 2018 (Arrêté du 12 Avril 2018 fixant la liste des recherches mentionnées au 2o de l'article L.1121-1 du code de la santé publique).
Germany	–	MS	+	–	NH studies with novel biomarker collections are not specifically regulated under German law and are classified as MS.
Israel	–	NI	+	–	
Japan	–	NI/INT	+	+	The study is NI if routine medical practice is followed, and INT if assessments fall outside of routine practice. NH studies fall under the Clinical Trials Act if they are commercially funded, which requires submission to both EC and RA.
Mexico	+	LI	+	+	Definition of LI: research with minimal risk; prospective studies that: use data risk through common procedures in physical or psychological examinations of routine diagnosis or treatment; research with commonly uses drugs with a wide therapeutic margin, authorized for sale, and using the indications, dosage, and administration routes established; and that are not medications currently under clinical research.
Netherlands	–	PR	+	–	NH studies with novel biomarker collections fall under the category of PR. PR that does not require a license fall under the WMO, and is required to be approved by the MREC.
Portugal	–	NI/INT	+	±	Study classifications to be evaluated on a case-by-case basis and depends on the level of intervention outside of routine practice. Specific submission to the central EC can be made to categorize as INT or NI if there is uncertainty. CEC approval applies to both INT and NI studies; however, all INT studies also require RA approval.
South Korea	–	NI	+	–	
Spain	+	LI	+	±	LI studies defined as research on marketed products used within the terms of the marketing authorization/CE mark or “off-label” indications that are well supported by published safety and efficacy data, or where a complementary diagnosis or follow-up procedures entail minimal risk or additional burden to subjects compared to routine clinical practice in any of the EU member states involved. RA submission is required for study classification.
Switzerland	–	NI/INT	+	±	Falls under HRO legislation if medical device and diagnostics are CE marked and will be used strictly according to the instructions for use, if not then the research falls under Clinical Trials Ordinance. Under HRO, studies are submitted for EC approval only, whereas under Clinical Trials Ordinance, both RA and EC approvals are required.
The UK	–	NI/INT	+	+	The study is NI if collection of biomarkers adheres to routine practice, and INT if nonroutine tests are performed Research involving nonroutine biomarker collection must be submitted to an MHRA for approval, as well as to ECs and HRAs.
Ukraine	–	INT	±	+	Collection of novel biomarkers would classify an NH study as INT. RA approval is required followed by notification only to ECs.
The USA	–	NI	+	–	

CE, Conformité Européenne; CEC, Centro europeu do consumidor; CONEP, Comissão Nacional de Ética em Pesquisa; EC, ethics committee; EU, European Union; HRA, Health Research Authority; HRO, Human Research Ordinance; INT, interventional; LI, low interventional; MHRA, Medicines and Healthcare Products Regulatory Agency; MREC, Medical Research Ethics Committee; MS, miscellaneous studies; NH, natural history; NI, noninterventional; PR, population research; RA, regulatory authority; WMO, Medical Research Involving Human Subjects Act.

were complemented by searches of the following official websites to evaluate current legislation:

- International Research Standards: International Compilation of Human Research Standards (<https://www.hhs.gov/ohrp/sites/default/files/2019-International-Compilation-of-Human-Research-Standards.pdf>).
- EU and EU Members States: EUR-Lex (<https://eur-lex.europa.eu>); N-Lex (<https://n-lex.europa.eu/n-lex/>).
- Argentina: Boletín Oficial de la República Argentina (<https://www.boletinoficial.gob.ar/seccion/primera>).
- Australia: Federal Register of Legislation (<https://www.legislation.gov.au>).
- Brazil: Portal da Legislação (<http://www4.planalto.gov.br/legislacao/>).
- Canada: Justice Laws Website (<https://laws.justice.gc.ca/eng/>).
- Israel: Gov.il (<https://www.gov.il/he/departments/legalinfo?skip=0&limit=10>).
- Republic of Korea: Ministry of Government Legislation National Law Enforcement Centre (<http://www.law.go.kr/LSW/eng/Main.do?eventGubun=060124>).
- Japan: Ministry of Education, Culture, Sports, Science, and Technology (MEXT) (<http://www.mext.go.jp/english/>); Ministry of Health, Labor, and Welfare (MHLW) (<http://www.mhlw.go.jp/english/index.html>).
- Mexico: Gobierno de México (<https://www.gob.mx>).
- Switzerland: The Federal Council (The Portal of the Swiss Government) (<https://www.admin.ch/gov/en/start/federal-law/search.html>).
- Ukraine: Legislation of Ukraine <https://zakon.rada.gov.ua/laws/main/en/index>.
- The UK: <http://www.legislation.gov.uk/>.
- The USA: Congress.gov (<https://www.congress.gov/#>); DHHS Office for Human Research Protections (OHRP) (<http://www.hhs.gov/ohrp/>).

Results

NH Studies: General Requirements

The authors evaluated the current legislation surrounding the classification of NH studies with genetic biomarker collections in 19 countries (Table 1). Three countries (16%) – France, Spain, and Mexico – stand out based on their legislation permitting the collection of minimally invasive samples to fall under the scope of low-intervention research. While Belgium, the UK, Portugal, Switzerland, and Japan (26%) did not precisely classify NH studies with prospective genetic testing, their categorization was deemed subjective as they may be interventional or noninterventional, depending on whether genetic testing and biomarker sample collection methods conform to routine clinical practice. The remainder of the examined countries classified NH studies with the collection of genetic information as either noninterventional (7 countries – 37%), interventional (2 countries – 11%;

Fig. 1. Classification of a subset of legislations surrounding NH studies with genetic biomarker collection. NH, natural history.

Ukraine and Brazil), or other (2 countries – 11%; the Netherlands and Germany) (Fig. 1).

It was also observed that EC approval was required in all countries apart from Ukraine, where only EC notification was required. On the other hand, the requirement for regulatory authority approval varied significantly; while 5 countries (26%) – France, Japan, the UK, Mexico, and Ukraine – required regulatory approval, 11 countries (58%) – Argentina, Australia, Brazil, Canada, Germany, South Korea, Belgium, Bulgaria, the Netherlands, Israel, and the USA – did not require any regulatory authority involvement, and 3 countries (16%) – Switzerland, Portugal, and Spain – had variable requirements depending on the legislation. Of the 11 countries where regulatory authority approval was not required, 7 (64%) categorized NH studies as noninterventional, 1 (9%) as interventional, 1 (9%) as noninterventional/interventional, and 2 (18%) as other.

Requirements for Genetic Testing in NH Studies

To assess the current regulatory landscape for genetic testing, the presence of regulatory requirements surrounding genetic testing and genetic counseling was evaluated in a subset of countries worldwide (Table 2). Of the 19 selected countries, 6 (32%) – Argentina, Australia, Brazil, the UK, Ukraine, and Belgium – had no specific regulatory provisions relating to genetic testing, and 11 (58%) did not have binding requirements for genetic counseling. Overall, 8 countries (42%) – France, Germany, Israel, Spain, Bulgaria, Mexico, Portugal, and Switzerland – had specific legislations covering both genetic test-

Table 2. Summary of regulatory frameworks for genetic testing in the context of NH studies

Country	Legislation covering genetic testing (+, yes; -, no)	Legislation covering genetic counseling (+, yes; -, no)	EC approval required (+, yes; -, no)	RA approval required (+, yes; -, no)	Biobank approval required (+, yes; -, no)	Signed and ratified Oviedo Convention (+, yes; -, no)	Signed and ratified "Additional protocol Oviedo Convention genetic testing for health purposes" (+, yes; -, no)	Comments
Argentina	-	-	+	-	-	-	-	
Australia	-	-	+	±	+	-	-	Studies that include genetic tests that are not approved for use in the country must be approved by the TGA.
Belgium	-	-	+	-	+	-	-	Genetic counseling is performed, but the approach to counseling can differ from one center to another in terms size and composition of the counseling team.
Brazil	-	-	+	-	±	-	-	Biobank approval is via CONEP. Approval applies to storage of samples for future testing, not to predefined testing. Research that includes genetic testing must be accompanied by a genetic counseling proposal, and costs for genetic must be covered by the researcher.
Bulgaria	+	+	+	-	+	-	-	Genetic testing is covered by regulation 38 from 20 August 2010 for the implementation of a medical standard "medical genetics".
Canada	+	-	+	-	-	-	-	The GNDA prohibits any person from requiring an individual to undergo a genetic test or disclose the results of a genetic test as a condition of providing goods or services to, entering into or continuing a contract or agreement with, or offering specific conditions in a contract or agreement with, the individual. Exceptions are provided for healthcare practitioners and researchers. The enactment provides individuals with other protections related to genetic testing and test results.
France	+	+	+	+	+	+	-	Genetic testing and the requirements for genetic counseling fall under the civil code and public health code. Genetic counseling can be performed by the physician ordering the test or genetic counselor.
Germany	+	+	+	-	+	-	-	The law governing genetic testing is the GenDG. Results with significant prognostic relevance must be discussed with the patient by the responsible medical specialist or genetic counselor.
Israel	+	+	+	+	+	-	-	Genetic information law, 5,761–2,000.
Japan	+	-	+	+	-	-	-	Genotyping studies fall under the Clinical Trials Act if they are commercially funded. Genetic counseling is covered under guidelines for human genome/gene analysis research.
Mexico	+	+	+	+	-	-	-	Genetic testing is covered by the Genomic Sovereignty Act 2008. Genetic counselor is not a recognized profession in Mexico. Provision for genetic counseling is limited.
Netherlands	+	-	+	+	-	-	-	Genetic research is covered by the Medical Research Involving Human Subjects Act (2006).
Portugal	+	+	+	+	+	+	+	Genetic testing is covered by Law 12/2005 of 26 January – personal genetic information and health information; and law decree 131/2014 of 29 August. Genetic counseling is via medical consultation by the physician responsible for the patient's treatment.
South Korea	+	-	+	+	+	-	-	All research involving genetic testing is classified as "research involving human subjects" under the Bioethics and Safety Act. In addition, patients and immediate family members are required to be counseled on the importance of the genetic testing, but there is no legal requirement. Biobank approval is required from the Ministry of Health and Welfare.
Spain	+	+	+	-	±	+	-	Genetic testing falls under the National law on biomedical investigations (Ley 14/2007, de 3 julio, de Investigación biomédica). Biobank approval is required if the biobank is located in Spain and not authorized by the Ministry of Health. New biobanks must be approved by the local government where the biobank is located.
Switzerland	+	+	+	±	+	+	-	Genetic testing is covered under the Federal Act on Human Genetic Testing (2004). Consultation by a qualified physician is required if the genetic testing has significant prognostic relevance and is not for research only. For predictive and prenatal genetic testing, genetic counseling is necessary before and after the analysis.

Table 2 (continued)

Country	Legislation covering genetic testing (+, yes; -, no)	Legislation covering genetic counseling (+, yes; -, no)	EC approval required (+, yes; -, no)	RA approval required (+, yes; -, no)	Biobank approval required (+, yes; -, no)	Signed and ratified Oviedo Convention (+, yes; -, no)	Signed and ratified "Additional protocol Oviedo Convention genetic testing for health purposes" (+, yes; -, no)	Comments
The UK	–	–	+	+	–	–	–	Research involving nonroutine genetic testing must be submitted to the MHRA for approval as well as to EC's and the HRA. No specific regulations exist for genetic counseling, but in practice, testing will not be performed unless there has been counseling.
Ukraine	–	–	±	+	–	–	–	
The USA	+	–	+	–	–	–	–	Genetic testing is covered under the GINA that prohibits discrimination with respect to access to health insurance and employment opportunities based solely on genetic predisposition to possibly developing a disease in the future. Genetic counseling is routinely performed but is not regulated by law. The CMS does not currently recognize genetic counselors as healthcare providers.

CMS, Centers for Medicare and Medicaid Service; CONEP, Comissão Nacional de Ética em Pesquisa; EC, ethics committee; GenDG, Human Genetic Examination Act; HRA, Health Reimbursement Arrangement; MHRA, Medicines and Healthcare products Regulatory Agency; RA, regulatory authority; NH, natural history; GINA, Genetic Information Nondiscrimination Act; GNDA, Genetic Nondiscrimination Act; TPA, Therapeutic Goods Administration.

ing and counseling. Of these, Mexico was the only country where genetic counseling had not been acknowledged as a recognized profession.

There was a consensus across all countries regarding the requirement for EC approval prior to genetic sample collection within a research setting, apart from Ukraine. However, regulatory agency opinion was determined to be compulsory in only 9 (47%) countries. Biobank approval was also determined to be necessary in 9 (47%) countries.

Several international bodies have published recommendations to guide and protect human rights in the field of genomic analysis and counseling [22–26]. Of particular interest is the “Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS No. 164)” [24], also known as the Oviedo Convention. This convention opened for signature in 1997 and is legally binding in 29 member countries of the Council for Europe, who signed and ratified the treaty to date. Its purpose is to provide the protection of human rights in the biomedical field. Of the representative sample, 4 countries (21%) – France, Spain, Portugal, and Switzerland – were ratified under the Oviedo Convention, with only Portugal having signed the additional Oviedo convention protocol specific to genetic testing.

Countries within Europe

To illustrate the divergence that exists currently among European countries with respect to the regulation of NH studies with novel genetic biomarker testing, 4 countries are compared and contrasted: Germany, Switzerland, Belgium, and the UK. Switzerland and Germany have legislation in relation to genetic testing that is closely aligned. Genetic examinations and diagnostic genetic tests can be ordered by any physician; however, predictive genetic tests must be arranged by a geneticist or a specifically trained medical doctor, and genetic counseling must be provided by law. In Germany, genetic counseling is required to be performed by a genetic counselor or medical specialist after the test has been performed; whereas in Switzerland, genetic counseling is required before and after predictive genetic testing is performed. If genetic testing has significant prognostic relevance, consultation by a responsible physician in addition to the genetic counselor is required. Neither country considers NH studies with nonroutine predictive biomarker testing to be low intervention; in both countries, these studies are only subject to review and approval by an EC. The exception to this in Switzerland is if a medical diagnostic device is not CE marked or will not conform strictly to the instructions for use, in which case the protocol will require regulatory and EC approval.

The UK and Belgium by contrast do not have specific legislation regarding genetic testing, and rules and norms are governed by nonbinding guidance documents. There is no distinction made between diagnostic and predictive

tests; however, predictive tests are generally ordered by senior medical doctors. Although there is no legal requirement for genetic counseling in either country, it is commonplace – in Belgium, it is carried out by multidisciplinary teams in 8 centers [27]. In the UK, genetic counseling is a requirement for any analysis and is routinely performed by genetic counselors. NH studies that include predictive nonroutine genetic testing are considered interventional in both countries and must be submitted to the National EC for approval in Belgium and for ethics and regulatory approval in the UK.

Countries within Asia Pacific

Outside of the EU, 2 contrasting countries are South Korea and Japan. In South Korea, NH studies involving predictive genetic testing are regarded as noninterventional and as such are subject to ethics approval only. However, Ministry of Health and Welfare approval is required for establishing a biobank. All research involving genetic testing is governed by the Bioethics and Safety Act 2013 [28]. Nonetheless, this does not include a legal requirement for genetic counseling, which is not structured within the country. By contrast, in Japan, NH studies involving predictive genetic testing are regarded as noninterventional or interventional research, depending on whether or not the assessment falls outside of routine clinical practice. NH studies that are commercially funded fall under the Clinical Trials Act of 2017 [29], which requires submission to the appropriate regulatory authority and EC(s). Without legislative instruments covering genetic counseling, the emphasis in Japan is on “self-regulation” in accordance with national guidelines.

Australia has not enacted any specific legislation regarding genetic testing for healthcare purposes, and much of the regulation of genetic testing is contained in general legislation, like the Therapeutic Goods Act of 1989 [30] and the Therapeutic Goods (Medical Devices) Regulations of 2002 [31], which defined all genetic tests as in vitro diagnostic devices. As such, studies that include genetic tests that are not approved for use in the country must be approved by the Therapeutic Goods Administration, as well as ECs. While genetic testing for medical purposes usually requires a referral from a medical practitioner, there are currently no uniform protocols for referral and no legal requirement for genetic counseling, which leads to an inconsistent approach [32].

Countries within North America

The legislative environment for NH studies with genetic biomarkers is broadly similar between the USA and Canada,

with neither country currently having specific legislation to cover genetic counseling and no remit for review or approval of these studies by their respective regulatory agencies. The main piece of legislation covering genetic testing in the USA is the GINA of 2008 [26], which is designed to prohibit discrimination with respect to access to health insurance and employment opportunities based solely on genetic predisposition to possibly develop a disease in the future. A similar piece of legislation came into effect in Canada, the Genetic Nondiscrimination Act (GNDA) of 2017 [33]. This, along with amendments in the Canadian Labour Code and the Canadian Human Rights Act, prevents companies and employers from requiring genetic testing or the results of genetic tests and prohibits them from denying services based on the results of genetic tests. Neither piece of legislation makes any provisions for who can order genetic tests or how they are communicated. In the USA, diagnostic testing can be ordered by any physician and may be returned to someone other than the doctor who ordered the test.

Countries within Latin America

Although the provision of genetic testing is increasing in the 3 largest Latin American economies (Brazil, Mexico, and Argentina), the scope and availability of genetic services in these countries currently lag behind North America and western Europe. The classification of NH studies with a predictive genetic testing component varies between the 3 countries, with Brazil classifying them as interventional, Argentina as noninterventional, and Mexico as low intervention, along the same lines as France and Spain. Mexico is the only country that requires submissions to the country’s regulatory agency before research can start. In Brazil and Argentina, only EC approvals are required. Genetic counseling is required by law in Mexico; however, counselors are not a recognized profession, and, for the most part, medical geneticists provide genetic counseling services. There is no legal requirement to perform genetic counseling in Argentina or Brazil. However, all research that includes genetic testing in Brazil must be complemented by a genetic counseling proposal, for which there is an obligation for the researcher to cover the costs of the subsequent counseling.

Discussion

Lack of Harmonization in the Classification of NH Studies with Novel Biomarker Collection

This review of the regulatory and legal landscape for NH studies involving the collection of novel biomarkers

demonstrates that there is a wide variation in how these studies are classified and regulated across the countries selected. In North America, the USA and Canada have designated such research as noninterventional and subject to institutional review board approval only as opposed to Mexico, where these studies are classified as low intervention and require both EC and regulatory authority approvals. In Europe, Spain and France have made provision of low-intervention research in their individual country legislation in line with EU Clinical Trial Regulation 536/2014, which includes a definition of low-intervention studies and which is expected to replace the Clinical Trials Directive 2001/20/EC in 2021. The inauguration of EU legislation that distinguishes between low-interventional and interventional research could, in time, result in greater harmonization of the rules for conducting clinical research across EU member states, as has occurred between France and Spain. Other countries may, in turn, follow suit and adopt legislation that aligns with Europe, further streamlining the planning and organization of NH studies globally.

Lack of Harmonization of Genetic Testing for Biomedical Research Purposes

The definition of genetic testing in legal documents within Europe and compared to the rest of the world is not standard. Many countries do not distinguish between genetic testing and genetic information [34]. Furthermore, the motives for performing genetic tests are diverse and include medical and nonmedical reasons; therefore, the regulation of genetic testing depends on the scope and context in which testing is performed. This makes regulation of genetic testing challenging in terms of what needs to be regulated, why, and what the regulation is endeavoring to protect. Although legally binding requirements for genetic testing are more common than nonlegally binding documents in the EU, the scope of legal documents regarding genetic testing varies among countries. Some place more emphasis on labor and insurance requirements, while others place more focus on aspects like biobanking, data protection, or healthcare aspects (e.g., prenatal or predictive testing). The latter are arguably of most interest to researchers of NH studies involving the collection of genetic biomarkers for rare diseases. While it may be an unrealistic expectation for a single regulatory instrument to cover all aspects of genetic testing, we believe that harmonized regulations for research purposes are needed. The primary reason that it has not been achieved to date within Europe is the lack of any clear provision for the regulation of genetic tests in current EU directives.

Although guidelines such as the ICH Good Clinical Practices (GCP) and the Declaration of Helsinki make provisions for the protection of human rights in biomedicine, the Oviedo Convention remains the only international, legally binding instrument on the protection of human rights in the biomedical field. It contains provisions for predictive genetic testing that limits the use to “tests that are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counseling.” Despite this, the legal provisions for predictive genetic testing among the 29 countries that have ratified the convention are not unified. An additional protocol to the Oviedo Convention concerning genetic testing for health purposes opened for signature in 2008 [35]. This covered all genetic testing performed for health purposes, with the exception of tests in the human embryo or fetus; although the additional protocol on genetic testing has been welcomed by professional bodies such as the European Society for Human Genetics, it has only been ratified by 6 countries (the Czech Republic, Montenegro, Norway, the Republic of Moldova, Portugal, and Slovenia). Until it is approved by the Council of Ministers and signed and ratified by all EU member states, it will not be enshrined into EU law and the current status quo of divergent legislation and regulation of genetic testing for healthcare purposes will continue. The new ICH guideline on genomic sampling and management of genomic data (E18) [36] provides much needed guidance on general principles of collection, processing, transport, storage, and disposition of genomic samples or data from interventional and noninterventional clinical studies. The guideline, which was adopted by the regulatory members of the ICH assembly on September 16, 2017, is being implemented by ICH regulatory bodies and could represent significant progress toward a more unified regulatory landscape.

Legislation covering genetic information nondiscrimination in North America could affect the use of genetic testing in NH studies. In the USA, GINA’s broad definition of genetic information as “any individual, information about – (i) such individual’s genetic tests, (ii) the genetic tests of family members of such individual, and (iii) the manifestation of a disease or disorder in family members of such individual,” has resulted in contrasting judicial interpretations with respect to genetic information and has raised the question as to whether it has actually achieved its objective of reducing the fear of genetic dis-

crimination and being effective in removing a major barrier to people undergoing genetic testing and participating in genetic research [37]. Furthermore, GINA exists alongside a patchwork of state legislation with varying provisions relating to genetic information that could feasibly further complicate genetic testing in NH studies in the USA. In Canada, the GNDA has also been controversial, immediately prompting a legal challenge by the Quebec provincial government on constitutional grounds, claiming that it unjustifiably impinged upon provincial powers.

Furthermore, although the USA was the first country to initiate genetic counseling as a profession some 50 years ago [38], the extent and quality of genetic counseling vary depending on the individual result. This situation is, to a large extent, related to the fact that the US Centers for Medicare and Medicaid Services do not recognize genetic counselors as healthcare providers, and as such, they are not reimbursed for counseling in the same way a physician would be paid. However, this may be set to change with the recent advent of the Access to Genetic Counselor Services Act of 2019 [39], which, if passed by congress, would provide those on Medicare access to genetic counseling.

The limited scope and availability of genetic services in the 3 largest Latin American economies (Brazil, Mexico, and Argentina) compared to Europe and North America is partially due to how health care is delivered in each country but also due to a historic lack of will to put medical genetics high on the political agenda. Brazil, Mexico, and Argentina have public healthcare systems intended to provide a basic level of health care, all of which are subject to financial and bureaucratic constraints. Brazil has a unified public health system that provides free health care for most of the population, but genetic testing funding has, for the most part, been limited to screening of newborns [40]. However, with the release of the National Policy for Rare Diseases of 2014, which defines the guidelines for offering treatment to individuals affected by rare diseases in the public health system, the scope of genetic services is expected to increase in the future. Argentina's public healthcare system is decentralized (with health services administered by provincial and municipal governments that operate independently), offering a varying range of healthcare services with genetic services low on the priority list, a situation that has been exacerbated by the lack of national guidelines for the provision of medical genetic services. However, in 2017, the Ministry of Science and Technology launched a funding initiative to develop the knowledge required to implement genomic

technologies in clinical practice; the impact this is going to have on the country's healthcare system remains to be seen. The Mexican government operates an elaborate tripartite public healthcare provision that provides fully or partially subsidized care, with private employer-sponsored and single-payer contributions based on employment status. For many, this means limited access to medical genetic services. Resources are concentrated mainly in the capital and focused on genetic and genomic research, rather than testing for clinical purposes [41].

Practical Implications for the Design and Conduct of NH Studies

One challenge in operationalizing studies in rare diseases is the enrollment of patients, as those affected may be hard to identify and incidence of disease is typically geographically dispersed [42]. To achieve target sample sizes, studies typically are conducted internationally and in the markets with the highest prevalence of a disease. Effective recruitment is supported by outreach to clinicians and the rare disease patient population through advocacy groups. Collaborative efforts with patient advocacy groups could be leveraged to create a common approach with regulatory bodies. However, without any global standard in regulations, multinational NH studies with a genetic biomarker element succumb to divergent local laws, approval pathways, and genetic service provisions that increase study complexity. These challenges include operational complexity, ethical considerations, regulatory authority submission logistics, and the resources required to run these studies.

Study-mandated genetic testing may contribute to higher research costs as local country requirements for genetic services must be adhered to. Genetic testing as part of routine clinical care is typically subsidized by governments or health insurance plans when it is recommended by a physician [43]. However, nonroutine predictive genetic tests outside of the standard care jurisdictions are unlikely to be covered by healthcare systems, suggesting that these costly, novel rare disease biomarker tests must be borne by research funding. Similar obligations may be requested for genetic counseling services if not offered through local services, as genetic consultation by a specifically trained medical healthcare provider or genetic specialist should be available to all patients and their families. This may need to include the ability to access future treatments as and when they enter clinical development.

Though NH studies are classified as noninterventional, the addition of a nonroutine genetic test to research being

Table 3. Summary of practical implications for the researcher and patient

	Implications for the researcher	Implications for the patient
Autonomy	Fully informed consent Test procedure Current biomarker analysis Future biomarker analysis Adequate provisions for assent and consent in minors	Rights to be informed or not of the results Rights to withdraw consent Same rights apply to minors
Transparency	Provision of genetic counseling strongly recommended when not legally required	Genetic counseling allows patients to discuss potential spouse/family implications
Access	Access to a treatment must be available, or in the absence of treatment, to clinical trials or registries	Impact on health insurance premiums and ability to access health care
Privacy	Apply regional and local data protection regulations related to genetic personal data	Rights related to regional and local data protection regulations

conducted in an NH setting may impact study classification. The classification of an NH study as interventional does not mean that GCP guidelines will need to be followed, if only because the purpose of the study is to describe the disease and not the effects of a drug. However, researchers may need to provide an insurance certificate and, in situations where a biomarker test is not yet approved, there may also be a requirement to submit a clinical trial medical device application for approval and report adverse events in the context of poor test performance (e.g., failing to detect the health risk for which it was designed).

The approval pathway for NH studies can be complicated by the addition of genetic testing, and this is particularly pertinent to NH studies in rare diseases (many of which have a genetic origin or component). The authors have recent experience of this in Australia, Israel, and Saudi Arabia, where the addition of a prospective genetic test to an NH study necessitated a submission of the protocol to the regulatory authorities in each country for approval, as well as ECs. This step was not anticipated in the initial study planning phase, but was required after consulting with the authorities to clarify their requirements. This illustrates that regulatory requirements for these studies are not always clear and that researchers should engage with regulatory bodies before proceeding.

In addition, the NH rare disease protocol should be clear regarding the study objectives, account for the small sample size scattered across multiple countries and sites, carry the appropriate methodology, and provide justification for genetic testing. To ensure study success, advocacy groups should be promptly engaged to provide input on study design and implementation [44]. Ethical considerations should be reflected in the study design and pro-

tol, including the plan for protection of personal data, privacy concerns of the patient's family members, and publication of the study results, which may render patients more easily recognizable, depending on to the rarity of the disease [44]. Since most rare diseases manifest in early childhood [45], there are added ethical considerations when enrolling children, such as obtaining informed consent from a legal guardian [46]. Practical challenges include obtaining blood sample specimens for genetic testing from children (low blood volume) in a way to minimize distress. Moreover, it is important that subsequent documents (such as consent forms) provide sufficient information for the patient (or caregiver) to make an educated decision about providing consent for the genetic test, and detail the implications of a positive test result for the patient and their family members. Data collection, biobank storage for future use, data privacy (e.g., General Data Protection Regulation in Europe), data anonymization, and sample destruction are also other points for consideration [46].

While there are responsibilities for researchers in relation to performing genetic testing during an NH study in rare diseases, there are also implications for the patient (Table 3). Patients have the right to withdraw consent at any time and choose whether to be informed of a genetic test result. While it may be argued that predictive genetic testing performed outside of routine clinical practice represents only minimal risk of burden to the patient, these results influence the future management of patients' disease or their perception of themselves or their condition. Identification of a genetic component may also lead to concerns about future reproductive planning or worries for the patient's family members [47].

In spite of this, the results of a genetic test may provide relief to a patient, introduce improvements to medical care, prevent misdiagnosis for family members, and provide patients access to advocacy groups [47]. Patients and their family members can benefit from the psychological support, comfort, expertise, disease education, and access to the latest treatment options through clinical trials that patient advocacy organizations can provide, which are all invaluable for patients diagnosed with a rare disease.

Conclusion

The era of precision medicine and biomarker-defined disease subsets is forging a new path in the clinical research and development landscape of rare and orphan diseases. Given that the majority of rare diseases presently do not have any specific treatment, the development of a new orphan drug would change the trajectory of the rare disease and simultaneously alter the patients' lives [48]. However, the implementation of genetic determination as a component of NH studies in rare diseases is not straightforward. The lack of harmonization across the regulatory landscape plays a large role in impacting the conduct of these studies – not all countries have ratified existing multinational frameworks, such as the Oviedo Convention and its protocols. Therefore, it is not surprising that there is a lack in consensus in genetic testing terminology and global variability in country-specific genetic service policy statements and guidelines. The additional cost pressure of genetic testing and counseling resulting from differences in regulations adds to an already costly drug development process. A set of international guidelines for the conduct of genetic testing in the context of NH studies would help harmonize the requirements for this type of research and improve the efficiency and quality of multinational studies in rare diseases. This may be on the horizon with the recent adoption of ICH guideline E18, but it remains to be seen how this will be incorporated into local regulations. However, we have been able

to elucidate examples of countries where ethical sound best practices for genetic testing/genome sequencing have been incorporated into local regulations (e.g., Germany and Switzerland). These examples provide guidance for researchers looking to adopt best practice for genetic testing in multinational NH studies.

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Statement of Ethics

Ethics approval is not required for this type of study as we did not access any direct patient data.

Conflict of Interest Statement

A.B., D.S., L.S., and F.K. are full-time employees of Evidera, the peri- and post-approval practice area of Pharmaceutical Product Development (PPD). M.R. was a full-time employee of Evidera at the time this work was performed. The authors have no conflicts of interest to declare.

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Author Contributions

A.B. contributed to the conception and design of the work, acquisition, analysis, and interpretation of data, as well as the preparation of the manuscript. D.S., M.R., and F.K. contributed to the conception and design of the work and to the interpretation of the data. L.S. contributed to the analysis and interpretation of data, as well as the preparation of the manuscript.

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