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Technological forecasting and regulatory assessment: An application to assisted reproductive technologies

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List of acronyms

ART – Assisted Reproductive Technologies

CRISPR/Cas - Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated

ICSI - Intra-Cytoplasmic Sperm Injection

IVF – In Vitro Fertilization

IVM – In Vitro Maturation of Oocytes

MNT - Mitochondrial Manipulation technologie

OCR – Oocyte Retrieval

PGD – Preimplantation Genetic Diagnosis

PGS – Preimplantation Genetic Screening

1. INTRODUCTION

1.1. Motivation

The understanding of technological diffusion is necessary both in order to induce innovation and to direct its trajectories to the public benefit. Diffusion of innovation is "the process by which an innovation is communicated through certain channels over time" (Rogers, 1983, p. 12). It is a multi-cycle, two-way process of communication between different agents in society. The study of this process requires observing the factors influencing it, such as innovation's relative advantage, compatibility with social values, levels of trialability, visibility, and complexity; in addition to the social structures, such as institutions, norms, and imaginaries (Rogers, 1983).

The diffusion of medical innovation is particularly complex, as such innovations implement solutions to emerging problems; solutions which are rarely presented as a final product or service, but are instead developed by trial and error, progressively improved, refined and extended in their scope of application (Barberá-Tomás & Consoli, 2012). Therefore, the design and implementation of new medical solutions depend also on the creation of a generally accepted scientific approach, based on an agreement between different professional groups (Teece, 1986; Barberá-Tomás & Consoli, 2012).

These agreements are often communicated through regulations and public procurement, which are set to deal with new technologies by providing responsible frames and institutions (Boon et al., 2015). Regulations are applied to correct inefficiencies or inequalities, information failures, and inadequate provision, as well as to reduce negative externalities and induce positive ones (Paraskevopoulou, 2012). The relationship between regulation and innovation is neither static nor single-directional; instead, it is reciprocal since regulation affects innovation and in turn, the outcomes of an innovation create new conditions to be regulated (Paraskevopoulou, 2012), and also alter the social values on which regulation is often based upon (Beck-Gernsheim, 2000).

Different supply and demand factors influence the diffusion of innovation since technological trajectories are always shaped not only by scientific advances but also by economic, social, and institutional factors (Dosi, 1982). The technology-push approach highlights the role of science and technology, stressing that advances in scientific knowledge determine the trajectories of innovation. However, the demand-pull perspective underscores market features and changes in customers' needs as the factors directing innovation toward the desired outcome. Therefore, the role of demand increases through the evolution of the technology's life cycle.

Indeed, the literature on technological change emphasizes that the process of innovation is not linear but interactive, as the technology and its users affect each other along the way (Walsh, 1983;

Nemet, 2009; Peters et al., 2012; Di Stefano et al., 2012). In this thesis, we approach the diffusion of Assisted Reproductive Technologies (ART) from the supply, demand, and regulatory perspectives, and analyze the interaction between these three components.

ART includes various methods involving the manipulation of both oocytes and sperm to assist human reproduction (CDC, 2018). Most commonly, it refers to In-Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI). In recent decades, the use of ART has proliferated, and it already accounts for over 5% of births in some leading countries (SEF, 2016; ESHRE, 2018; Ishihara, 2019).

Since ART involves the fertilization of human embryos in-vitro, it allows conducting Preimplantation Genetic Diagnosis or Screening (PGD/PGS) by removing a biopsy from each embryo to detect genetic mutations (PGD) or chromosomal abnormalities (PGS). These techniques allow avoiding transferring an embryo with a severe genetic disorder (PGD) or serve to increase treatment prospects by choosing euploid embryos (PGS), i.e., those who carry a correct number and structure of chromosomes.

The use of reproductive genetics is becoming common; in 2016, it took part in 22% of all IVF cycles in the U.S. (CDC, 2018). Additionally, in recent years, genetic engineering of human embryos by CRISPR/CAS has developed substantially, and it seems to be a matter of time until it will be regularly introduced for clinical use. Most recently, the use of CRISPR/CAS has caught the world's attention with the announcement of the first birth of genetically edited babies in China in December 2018 (Krimsky, 2019).

ART is a growing industry, currently mainly due to infertility, which according to different studies, amounts to 10-15% of the general population (Evers, 2002; Spar, 2006; Agarwal et al., 2015; ASRM, 2015). Some evidence shows that this share is increasing, due to the rising age of parenthood, environmental factors and lifestyle (Boivin et al., 2007; Mascarenhas et al., 2012; Johnson, 2014; Inhorn & Patrizio, 2015; Sobotka, 2016). It is also becoming more common among single women, lesbians, and gay male couples. At the same time, reproductive genetics is becoming a growth factor too, and not less important, it is more frequently being added to IVF cycles.

Medical technology is marked by many as one of the most promising S&T areas in the 21st century, where increasing innovative efforts promise to extend human life and improve human well-being (Amir-Aslani & Mangematin, 2010; Harari, 2016; Godinho, 2016). In the previous century, medicine defined normal levels of health and medical policy and, in most countries, aimed at providing the majority of the public with health leveled according to these norms. However, in the 21st century, many medical innovations are aiming at surpassing these norms to produce an enhanced human (Silver, 1997; Fukuyama, 2003; Harari, 2011, 2016).

In this context, ART is raising high expectations by enabling the extension of reproductive age, and through the introduction of reproductive genetics, which allows preventing diseases from the outset, and could even lead to enhancing the human race. The idea that human reproduction might increasingly shift into the lab where genetic manipulations of many sorts can be conducted has produced many hopes but also preoccupations. Many works in the fields of humanities and social sciences, as well as non-academic literature, have dealt with the implications of ART over individuals and society. ART may change the way human reproduce and, as a result, in a more distant perspective, might even change the human race itself (Lewis, 1943; Ramsey, 1972; Silver, 1997; Shulman & Bostrom, 2014; Greely, 2016), which raises questions regarding accessibility, equity, social justice and inclusiveness (Rawls, 1993; Paunov, 2013). Notably, the quest for the perfect baby raises many more ethical inquiries regarding embryo status, personal autonomy, parental responsibility, eugenics and social risks (Buchanan et al., 2000; Beck-Gernsheim, 2000; Habermas, 2003; Sandel, 2004).

Expectations, imaginaries, and fears occupy a pivotal role in the innovation process by shaping its potential, particularly during the early stages when technology is under large uncertainty (Brown & Michael, 2003; Borup et al., 2006). Since ART, and particularly reproductive genetics, develop and diffuse slowly, expectations and concerns continuously accompany the social debate and the regulatory process and may differ between communities based on different values and knowledge (Borup et al., 2006).

Interpretative flexibility of expectations often arises from asymmetries in access to information, as uncertainties of laboratory science are usually invisible to the broader public (Brown & Michael, 2003). There is, therefore, a knowledge gap between the science of ART and its philosophy concerning the IVF procedure, deriving from the complexity of the techno-scientific knowledge and the speed of technological progress (Marchant, 2011), which is influenced by numerous innovations in techniques, devices, and medicines. Also, there is a wide gap concerning genomics, an even more complex field of many uncertainties.

Another disparity in understanding the potential trajectories of ART stems from the large differences in regulations between different jurisdictions. In some countries, ART is strongly regulated through legislation and public funding while in others a laxer regulation is being conducted based on voluntary guidelines (Johnson & Petersen, 2008; Chambers et al., 2009; Brigham et al. 2013).

Analyzing expectations is a critical element in understanding scientific and technological change (Borup et al., 2006). This thesis aims to reduce the above-mentioned knowledge gaps by conducting technology forecasting and regulatory assessments based on Delphi surveys. It also aspires to provide

some light to enable making strategic decisions regarding the future (Brown & Michael, 2003; Borup et al., 2006).

1.2. Objectives and research questions

Our general objective is to assess the trajectories of ART and its pace of diffusion by identifying the factors that influence this process. This general objective can be split into the following specific objectives:

Our first goal was to conduct a technology forecasting in order to better understand the potential developments in IVF, PGD, and genetic engineering. This initial research question was influenced by the extensive literature describing a future in which reproduction would mainly be practiced by IVF accompanied with embryo selection or genetic engineering, to produce healthier and enhanced offspring (Silver, 1997; Savulescu, 2001; Harris, 2007; Murphy, 2014; Greely, 2016). Much of this referred literature is based on expectations concerning the remarkable or dangerous implications of such a trend. However, those opportunities and risks can be considered purely speculative if they are not grounded in a likely future. Therefore, we began by questioning the viability of these assumptions and the technical requirements for their materialization.

The second objective was to identify the factors affecting regulation and priority setting regarding ART and to review the responses to technological and market developments in the field, through a regulatory assessment and a comparative analysis between Israel and Spain (Ho et al., 2016; Hofer et al., 2015). Here we mainly focused on IVF and its present implications on society. We approached the diffusion of ART as a long process, influenced by today's choices in ART clinics and by public policies. It was a central objective of this thesis to analyze the strengths and flaws of regulation and provision, and its impact over individuals and society. This comparative analysis was inspired by previous works from the U.S., Canada, the U.K., and other European countries (Nelson, 2006; Brigham et al., 2013; Pennings et al., 2014; Präg & Mills, 2017; Jasanoff & Metzler, 2018).

Our final objective was to assess the regulatory trends that may (or not) lead to the "geneticization" of reproduction (Lippman, 1991), i.e., the shift of reproduction into the lab due to the ability to select or design genetic traits of embryos. This goal mainly focused on reproductive genetics and the regulatory response to potential futuristic developments. Moreover, it supplements the first goal since, in the field of ART, regulation plays a key role by interacting with both supply and demand. The combination of the two objectives, technology forecast and assessment of regulatory trends, allows us to get a better observation on the potential ART trajectories.

These three sub-objectives define the structure of this thesis around three chapters, which have been drafted as independent papers to be published in scientific journals (see also section 1.4 below).

Despite the focus on ART, this thesis also contributes to the broader field of diffusion of innovation and technology, predominantly in the field of medicine, by using qualitative methods through Delphi studies and in-depth interviews to evaluate technological developments and market trends, and by jointly analyzing supply, demand, regulation and the interactions between them (Nemet, 2009; Adner, 2015; Hammarberg et al., 2016). It represents a novel empirical approach, which might inspire future studies dealing with the diffusion of medical technologies.

1.3. Methods

We began by elaborating a theoretical framework based on an extensive literature of an inter-disciplinary character. Summaries of the literature form the second section of each paper presented in chapters 2-4 and provide rich contents which may contribute to future studies. Chapter 2 begins with a background section which serves as an introduction to the field of ART, including the technical settings and the bioethical context, which leads to our first research question. Moreover, the analytical framework presented in chapter 3 classifies the critical dimensions of national ART regulations and identifies the factors which may explain different regulatory choices. It provides a useful set of categories for further analysis in different countries. In chapter 4, the hypothesis that reproduction is going through a process of geneticization was examined, by dismantling the factors required for its realization and classifying them in three categories: supply, demand, and regulation.

Our empirical analysis was mainly based on the Delphi method, a widely used qualitative method for forecasting, assessment, and decision making regarding complex problems. It is developed through a quantitative survey in an anonymous and interactive process. A Delphi is built on a panel of experts who contribute with their knowledge, experience, and judgment to replace traditional statistical models and provide adequate sets of data when those are not available (Landeta et al., 2008; Salazar-Elena et al., 2016). The survey must be conducted in at least two rounds, to produce iteration following controlled feedback, allowing the experts to change their replies or add comments after learning the general views (Landeta & Barrutia, 2011; Von der Gracht, 2012; Mayor et al., 2016). The Delphi process allows experts to reach consensus or to build divergent scenarios (Landeta, 2002; Okoli & Pawlowski, 2004; Melander, 2018).

We applied the Delphi method through two different surveys to extract knowledge from physicians, public officials, researchers and other service providers, whose careers are dedicated or closely related to ART. Confronting these experts experience with the expectations raised in academic philosophical debates serves to engage with the future as an analytical object, introduce realism into the discussion, and reduce the confusion produced by inflated hopes and dystopian scenarios (Brown & Michael, 2003).

We focused on Israel and Spain, which are among the largest users of ART worldwide and can be characterized as "early adopters" (Rogers, 1983) of ART services. In the last decade, the total number of IVF cycles per year in Spain has increased remarkably, and according to most recent reports, it is the largest ART industry in Europe and third in the world (SEF, 2016; CDC, 2018; ESHRE, 2018, Ishihara, 2019). Israel is the largest ART industry in relative terms, partly due to its very comprehensive public coverage. Additionally, both countries have very supportive attitudes towards reproductive genetics, and PGD is practiced more commonly and with a larger portfolio than in most States (Pavone & Arias, 2012; Zlotogora, 2014; Zuckerman et al., 2017). Overall, Israel and Spain are currently among the most advanced countries with respect to ART, which makes them adequate targets for our empirical study.

As an important component of empirical data collection, 44 in-depth interviews preceded the two Delphi surveys. Meetings of one hour on average with the experts assisted in updating and validating the knowledge obtained through the literature review. These professional experts are well informed of the latest literature in their fields, and many of them also contribute to scientific publications. The interviews were semi-structured and open to allow the experts directing the research to some points of interests which they identified as important. As a result, the questionnaires were also designed based on the interest and focus shown by the interviewees, and the comments registered from interviews enriched the analysis with qualitative insights to better explain the quantitative results of each survey.

Subsequently, two Delphi exercises were conducted, each involving a different panel of experts which were consulted in two rounds. The first was undertaken between September 2016 and June 2018 and addressed 25 gynecologists and geneticists from elite clinics, 13 from Spain and 12 from Israel. The experts were questioned regarding developments in various technologies used for IVF, success rates and treatment possibilities, genomics, and genetic engineering and, finally, regarding demand forecast and attitudes towards regulation in a twenty years' horizon. The second Delphi was conducted between October 2017 and January 2019 and addressed two groups of 18 experts each, formed to simulate typical bioethics committees from Israel and Spain. The survey had two sections, one assessing the regulation of ART and its current framework, and the other focused on the regulation of different applications of reproductive genetics.

The two Delphi surveys partially approached similar issues with similar questions, although they addressed different types of experts. It allowed us to stand on the differences between suppliers (in our case, physicians) and regulators. While our methodological approach to ART can be directly practiced in other countries and different groups of experts, it could also be adapted to other fields of medical innovations, where the interactions between supply and demand are strongly influenced by regulation and public financing. The two questionnaires are annexed at the end of the thesis.

This methodological approach, however, is not exempt from limitations. The use of the Delphi method based on experts always has a level of subjectivity, concerning the definition of an expert and the factors biasing his/her opinion (Devaney & Henchion, 2018). Therefore, different experts may express different attitudes, which could also direct the study to different focuses. It would also be interesting to contrast our results against other collectives, including various kinds of stakeholders (e.g., patient associations, hospital managers and non-practitioner scientists). Moreover, our selection of two countries in an advanced stage of diffusion, with very pro-ART attitudes and which tend to nourish a comprehensive public healthcare system, may produce some biases. Therefore, the forecast and the regulatory assessment provided for Israel and Spain might not represent the global scenario. A selection of different countries in earlier stages of ART, with a strong attachment to individualized and free-market economic theories (such as the USA) (Johnson & Petersen, 2008), or where the use of reproductive genetics is contested (i.e., Austria or Germany) (Hashiloni-Dolev & Raz, 2010; Griessler & Hager, 2017), could lead to different results.

Finally, the reliability of forecasting is always limited due to the field's complexity. Many developments in genomics, prenatal testing and medicine could affect the trajectory of ART. Moreover, the technology course is influenced by a broader range of related aspects, such as regulations, institutional and economic factors, consumer choices and pressures from different interest groups, which might be hard to capture (Brigham et al., 2013; Martin, 2014). Nevertheless, the experts who participated in the first Delphi are leading gynecologists and geneticists in Israel and Spain who have practiced IVF and PGD for many years, and their countries are at the forefront of the world's ART industry. Indeed, many of the predictions introduced by the panels are compatible with recent literature (Lu et al., 2016; Casper et al., 2017; Nuffield Council on Bioethics, 2018), which substantiates the robustness of our methodological approach.

1.4. Structure of the thesis

The contributions of this dissertation are presented in three papers (corresponding to chapters 2-4), as shown in Table 1. The first describes a technology forecast based on the first Delphi, the second introduces a regulatory assessment of Israel and Spain based on the second Delphi, and the third deals with the diffusion of innovation in light of the geneticization thesis and is based on a few questions from both Delphi surveys.

Title	Objectives	Method	Findings	Status
1. What to expect from assisted reproductive technologies? Experts' forecasts for the next two decades	To analyze technology and demand trajectories in ART with a 20 years horizon. We tested the viability of conducting an expanded PGD and using genetic engineering, and assessed the ethical limits of physicians regarding the use of ART.	17 semi-structured interviews. A Delphi survey with 25 Physicians, 12 Israelis and 13 Spanish.	A substantial increase in birth rates per IVF cycles. A limited improve in quantity of eggs, hence limits to expanded PGD. A greater potential in CRISPR/CAS for genetic engineering of human embryos. A steady increase in demand for IVF towards 16% of the population. The physicians rejected the use of ART for non-medical reasons.	Under second round of review in Technological Forecasting and Social Change (Elsevier). This journal has an Impact Factor of 3.815 (Q1).
2. Regulatory responses to Assisted Reproductive Technology: A comparative analysis of Spain and Israel	To propose a conceptual framework to facilitate cross-country comparisons on ART regulations and factors influencing regulatory choices. To conduct a regulatory comparison between Israel and Spain. To assess strengths and weaknesses in the countries' regulations and outcomes.	27 semi-structured interviews. A Delphi survey with 36 experts from various fields related to ART, comparing two panels of 18 Israelis and 18 Spaniards. Also based on results of first paper.	Both markets are largely driven by age-related infertility. In Spain it is due to the postponement of parenthood, which ends up with an excessive use of donor-eggs. In Israel it is the public funding norms which pushes women in their late fertility age to repeat multicycles with their own eggs. In both market the private-commercial interest as an excessive impact over regulations at the expense of health and ethical interests.	Accepted for publication in the Journal of Assisted Reproduction and Genetics (Springer) on June 2019. This journal has an Impact Factor of 2.820 (Q1).
3. Contesting the geneticization thesis in human reproduction: insights from Israel and Spain	To question the diffusion of ART from both supply, demand and regulatory aspects and to draw scenarios for the industry's trajectory in light of the geneticization thesis.	Combining the methodologies of the previous two papers in order to provide forecasts and build scenarios.	We may expect a continuous and steady growth in the use of ART, supplemented by reproductive genetics, including the introduction of CRISPR. Further diffusion must be based on reproductive genetics, and the industry might face limitation in	To be submitted to Science, Technology and Human Values (SAGE). Impact Factor 3.160 (Q1)

			supplying such services to a wide public. The regulation of ART is becoming more critical and complex, should ensure good practices and equity, and also provide more information to the public. A broad and inclusive societal debate may assist in drawing a line between medical uses and non-medical uses of reproductive genetics.	

1.5. Resumen en español (Summary in Spanish)

Motivación

La comprensión de la difusión tecnológica es necesaria tanto para inducir la innovación como para dirigir sus trayectorias hacia el beneficio público. La difusión de la innovación es un proceso de comunicación multi-cíclico y bidireccional entre diferentes agentes de la sociedad (Rogers, 1983). Por su parte, la difusión de las innovaciones médicas es particularmente compleja, ya que tales innovaciones implementan soluciones que raramente se presentan como un producto o servicio final, sino que se desarrollan por ensayo y error, se mejoran progresivamente, se refinan y se extienden en su ámbito de aplicación (Barberá-Tomás & Consoli, 2012). Por lo tanto, el diseño y la implementación de nuevas soluciones médicas también dependen de la existencia de un enfoque científico generalmente aceptado, basado en acuerdos entre diferentes grupos profesionales (Teece, 1986; Barberá-Tomás y Consoli, 2012).

Estos acuerdos a menudo se conforman a través de regulaciones y contratación pública, que se establecen para tratar con las nuevas tecnologías proporcionando marcos e instituciones responsables (Boon et al., 2015). Además, diferentes factores de oferta y demanda influyen en la difusión de la innovación, ya que las trayectorias tecnológicas siempre están moldeadas no solo por los avances científicos sino también por factores económicos, sociales e institucionales (Dosi, 1982). Así, el enfoque del empuje tecnológico ("technology-push") se centra en el impacto que ejercen la ciencia y la tecnología, mientras que la perspectiva de la demanda ("demand-pull") subraya las características del mercado y los cambios en las necesidades y preferencias de los clientes.

De hecho, la literatura sobre el cambio tecnológico enfatiza que el proceso de innovación no es lineal sino interactivo, ya que la tecnología y sus usuarios actúan de manera interrelacionada (Walsh, 1983; Nemet, 2009; Peters et al., 2012; Di Stefano et al., 2012). Por este motivo, en la presente tesis abordamos la difusión de las Tecnologías de Reproducción Asistida (TRA) desde las perspectivas de la oferta, la demanda y la regulación, analizando la interacción entre estos tres componentes.

Las TRA incluyen varios métodos que implican la manipulación de ovocitos y espermatozoides, que se emplean como ayuda para la reproducción humana (CDC, 2018). Más comúnmente, cuando se habla de TRA suele hacerse referencia a la fertilización in vitro (FIV) y la inyección intracitoplasmática de espermatozoides (o ICSI por sus siglas en inglés - "intracytoplasmic sperm injection"-), que ya representan más del 5% de los nacimientos en algunos países (SEF, 2016; ESHRE, 2018; Ishihara, 2019). Adicionalmente, las técnicas de reproducción asistida permiten la realización de procedimientos de genética reproductiva mediante el diagnóstico o cribado genético preimplantacional (DGP/CGP), cuyo uso también se está haciendo más común. Así, estos procedimientos se aplicaron en el 22% de todos

los ciclos de FIV que tuvieron lugar en Estados Unidos en el año 2016 (CDC, 2018). Además, en los últimos años la investigación en ingeniería genética a través de la técnica CRISPR/Cas de embriones humanos (del inglés "clustered regularly interspaced short palindromic repeats") se ha desarrollado sustancialmente, y parece ser solo una cuestión de tiempo hasta que se generalice su uso clínico. De hecho, el empleo de esta técnica ha llamado la atención del mundo entero con el controvertido anuncio, en diciembre de 2018, del primer nacimiento de bebés modificados genéticamente en China (Krimsky, 2019).

La industria de las TRA está experimentando un fuerte crecimiento, actualmente vinculado en su mayor parte al fenómeno de la infertilidad que, según diferentes estimaciones, afecta al 10-15% de la población humana (Evers, 2002; Spar, 2006; Agarwal et al., 2015; ASRM, 2015). Algunos estudios muestran que su incidencia está aumentando como consecuencia del retraso en la maternidad/paternidad, los factores ambientales, los estilos de vida y otros factores sociales (Boivin et al., 2007; Mascarenhas et al., 2012; Johnson, 2014; Inhorn & Patrizio, 2015; Sobotka, 2016). Al mismo tiempo, la genética reproductiva también está experimentando un crecimiento y se emplea cada vez con mayor frecuencia en los ciclos de FIV.

Muchos consideran que la tecnología médica es una de las áreas más prometedoras del ámbito científico-tecnológico del siglo XXI, donde los esfuerzos innovadores prometen extender la vida y mejorar el bienestar humano (Amir-Aslani y Mangematin, 2010; Harari, 2016; Godinho, 2016). En el siglo anterior, la Medicina contribuyó a establecer estándares de salud hoy considerados aceptables, y la política sanitaria de la mayoría de los países tuvo como objetivo garantizar dichos estándares para la mayoría de la población. Sin embargo, en el siglo XXI muchas innovaciones médicas apuntan hacia su superación mediante la creación de seres humanos mejorados (Silver, 1997; Fukuyama, 2003; Harari, 2011, 2016).

En este contexto, las TRA están generando altas expectativas al permitir la prolongación de la edad reproductiva y la prevención de enfermedades desde el momento de la concepción, e incluso la mejora de la raza humana a través de la introducción de la genética reproductiva. Numerosos estudios en los campos de las humanidades y las ciencias sociales, así como la literatura no académica, han abordado las implicaciones de las técnicas de reproducción asistida en los individuos y la sociedad. Las TRA pueden cambiar la forma en que se reproducen los humanos y, como resultado, en un futuro más lejano, incluso podrían modificar la raza humana (Lewis, 1947; Ramsey, 1972; Silver, 1997; Shulman & Bostrom, 2014; Greely, 2016). Esta posibilidad plantea muchos interrogantes sobre las posibilidades de acceso a dichas técnicas, la equidad en su utilización y la justicia social (Rawls, 1993; Paunov, 2013), así como sobre el uso de los embriones, las posibilidades de autonomía personal, la responsabilidad

parental, la eugenesia y otros riesgos sociales (Buchanan et al., 2000; Beck -Gernsheim, 2000; Habermas, 2003; Sandel, 2004).

Las expectativas, los imaginarios y los temores sociales ocupan un papel fundamental en el proceso de innovación al configurar su potencial, particularmente durante las etapas iniciales, cuando la tecnología está aún sometida a una gran incertidumbre (Brown y Michael, 2003; Borup et al., 2006). Dado que las TRA, y en particular la genética reproductiva, se desarrollan y difunden lentamente, las expectativas y preocupaciones acompañan al debate social y al resultado regulatorio a lo largo de todo el proceso (Borup et al., 2006). La diversidad con la que se interpretan las expectativas a menudo tiene su origen en las asimetrías informativas, ya que la incertidumbre que se vive en el laboratorio generalmente no se traslada al público general (Brown y Michael, 2003).

Otra parte de las diferencias que surgen en el análisis de las trayectorias potenciales de las TRA se deriva de la gran disparidad que se produce en la regulación internacional. En algunos países las TRA están fuertemente reguladas, mientras que en otros se está llevando a cabo una regulación más flexible basada en directrices de carácter voluntario (Johnson & Petersen, 2008; Chambers et al., 2009; Brigham et al. 2013). En esta tesis, nuestra principal ambición es la de reducir la brecha de conocimiento entre los aspectos científicos y sociales de las TRA, que en buena parte se deriva de la complejidad del conocimiento tecnocientífico y de la velocidad del progreso tecnológico (Marchant, 2011).

El análisis de las expectativas es un elemento crítico para comprender el cambio científico y tecnológico (Borup et al., 2006). En esta tesis realizamos previsiones tecnológicas y evaluaciones regulatorias basadas en el método Delphi, con la aspiración de proporcionar alguna información valiosa que permita la toma de decisiones estratégicas con respecto al futuro (Brown y Michael, 2003; Borup et al., 2006). El estudio se centra en Israel y España, dos países que cumplen condiciones óptimas para este tipo de análisis.

Objetivos

Nuestro objetivo general es evaluar la posible trayectoria que seguirán las tecnologías de reproducción asistida y su ritmo de difusión, identificando los factores que influyen en este proceso. Este objetivo general se puede dividir en los siguientes objetivos específicos:

1. Llevar a cabo un ejercicio de previsión tecnológica que contribuya a comprender mejor los desarrollos potenciales en el ámbito de la FIV, el DGP y la ingeniería genética, y permita asimismo cuestionar la viabilidad de algunos escenarios, así como los requisitos técnicos para su materialización.

2. Identificar los factores que afectan a la regulación y el establecimiento de prioridades, y realizar una evaluación regulatoria mediante un análisis comparativo de Israel y España, revisando las respuestas a los desarrollos tecnológicos y de mercado en este ámbito (Ho et al., 2016; Hofer et al., 2015).

3. Evaluar las tendencias que pueden conducir a la “genetización" de la reproducción (Lippman, 1991), es decir, el proceso por el cual la reproducción tendría lugar mayoritariamente en el laboratorio, debido a la capacidad técnica para seleccionar o diseñar rasgos genéticos de los embriones.

A pesar de centrarse en las técnicas de reproducción asistida, esta tesis también contribuye al campo más amplio de la difusión de la innovación y la tecnología (principalmente en el campo de la Medicina), mediante el uso de métodos cualitativos a través de la combinación de estudios Delphi y entrevistas en profundidad, que permiten evaluar los avances tecnológicos y las tendencias del mercado, analizando conjuntamente la oferta, la demanda, la regulación y las interacciones entre estos tres factores (Nemet, 2009; Adner, 2015; Hammarberg et al., 2016). De este modo, la tesis presenta un enfoque empírico novedoso que podría inspirar futuras investigaciones sobre la difusión de tecnologías médicas.

Métodos

Comenzamos elaborando un marco teórico que toma como base una extensa literatura de carácter interdisciplinar. La revisión de la literatura compone el segundo apartado de cada uno de los capítulos 2-4, y proporciona información muy útil que puede contribuir a futuros estudios.

Nuestro análisis empírico está basado principalmente en el empleo del método Delphi, un método cualitativo ampliamente utilizado para pronosticar, evaluar y tomar decisiones sobre problemas complejos (Landeta et al., 2008; Von der Gracht, 2012; Mayor et al., 2016; Melander, 2018). El Delphi se basa en un panel de expertos que contribuyen con su conocimiento, experiencia y juicio al análisis de un problema, lo que permite reemplazar los modelos estadísticos tradicionales cuando los conjuntos adecuados de datos cuando no están disponibles. Para desarrollar un Delphi se precisa recabar las opiniones de los expertos mediante una encuesta cuantitativa, en un proceso anónimo e interactivo de al menos dos rondas (Landeta, 2002; Okoli & Pawlowski, 2004; Landeta & Barrutia, 2011; Salazar-Elena et al., 2016).

Aplicamos el método Delphi para extraer el conocimiento de médicos, funcionarios públicos, investigadores y otros proveedores de servicios, cuyas carreras están dedicadas o relacionadas con las técnicas de reproducción asistida. Confrontar la experiencia de estos expertos con las expectativas planteadas en los debates filosóficos académicos sirve para tratar el futuro como un objeto analítico

(Brown y Michael, 2003), introducir realismo en la discusión y reducir la confusión producida tanto por las expectativas exageradas como por el temor a los escenarios distópicos.

Nos centramos en dos países, Israel y España, que se encuentran entre los usuarios más frecuentes de las TRA en todo el mundo y que pueden caracterizarse como "adoptadores tempranos" (Rogers, 1983) de estas técnicas, con actitudes muy favorables hacia la genética reproductiva (Pavone y Arias, 2012; Zlotogora, 2014; Zuckerman et al., 2017). En general, Israel y España se encuentran actualmente entre los países más avanzados con respecto al empleo de las TRA, por lo que pueden considerarse muy adecuados para nuestro estudio empírico.

Con carácter previo a las encuestas, realizamos 44 entrevistas con expertos de muchos campos relacionados con las TRA. Las entrevistas fueron semiestructuradas, lo que permitió a los expertos dirigir la investigación hacia algunos puntos de interés que identificaron como importantes. Como resultado, las encuestas también se diseñaron en función del interés y la perspectiva de los entrevistados, y los comentarios registrados en las entrevistas permitieron enriquecer el análisis con información cualitativa, lo que contribuyó a explicar mejor los resultados cuantitativos obtenidos de cada encuesta.

Llevamos a cabo dos ejercicios Delphi. El primero de ellos se centró en la evolución previsible de distintos aspectos tecnológicos y en el pronóstico de la demanda de TRA, y se basó en un panel de 25 ginecólogos y genetistas de clínicas de élite de Israel y España. El segundo Delphi recabó las opiniones de dos grupos de 18 expertos cada uno, seleccionados para simular los comités de bioética típicos de Israel y España, y tuvo como objetivo evaluar la regulación actual de las TRA y el parecer de los expertos acerca de diferentes aplicaciones de la genética reproductiva.

Resultados

Si bien cada uno de los tres capítulos centrales de la tesis contiene un análisis específico que conduce a distintos hallazgos, resumimos aquí algunos de los resultados más importantes. Nuestro análisis anticipa un aumento continuo en la proporción de nacimientos derivados de la FIV en Israel y España, y en el uso del DGP como un factor que aumenta por sí mismo la demanda de FIV y que, además, se utiliza como un complemento. Por su parte, el CRISPR/Cas bien podría practicarse de forma habitual relativamente pronto; sin embargo, pueden pasar años hasta que se comprendan todos sus posibles efectos adversos. Por lo tanto, el uso del CRISPR/Cas también podría verse limitado durante un período de tiempo prolongado (Evitt et al., 2015; Nuffield Council on Bioethics, 2018).

Identificamos que el factor más importante que induce la demanda de TRA en Israel y España es la infertilidad relacionada con la edad. En España, este fenómeno ha sido descrito como "infertilidad estructural" (Marre, 2009; Marre et al., 2018). Este hecho se relaciona con las condiciones socioeconómicas del país, que están llevando a muchas mujeres y hombres a posponer la maternidad/paternidad a una edad en la que a menudo se necesita utilizar técnicas de reproducción asistida, con una elevada probabilidad de que se requieran óvulos de donantes. En Israel, el entorno cultural, político y social está configurando las opiniones del público sobre la infertilidad, las técnicas de reproducción asistida y la relación genética. Así, una parte de los israelíes se somete a numerosos ciclos de FIV, que se financian con fondos públicos hasta los 44 años, intentando cumplir su deseo de formar familias numerosas y dar a luz a niños genéticamente relacionados (Birenbaum-Carmeli y Dirnfeld, 2008; Birenbaum-Carmeli, 2010).

La utilización de óvulos de donantes como solución a la infertilidad es un asunto importante y en crecimiento en España, y también un fenómeno en crecimiento en Israel, a pesar de que la mayoría de las donaciones provienen del extranjero. El mercado de óvulos plantea muchas controversias éticas. Además, dentro de unas pocas décadas, y como consecuencia del anonimato exigido en los registros de donantes, cientos de miles de personas (también debido a la donación de esperma) no tendrán acceso a la información genética, historia clínica e identidad de uno (o ambos) de sus padres biológicos, lo que puede ser fuente de una gran desventaja.

Otro tema controvertido en ambos países es la práctica del cribado genético preimplantacional (CGP), cuya eficiencia aún no se ha demostrado. No obstante, el uso del CGP implica tomar una biopsia de un embrión, lo que también podría allanar el camino para un aumento significativo en el uso del DGP, al convertir la detección de anomalías cromosómicas en una exploración de grandes partes (o la totalidad) del exoma, permitiendo así detectar mutaciones.

Por otra parte, a largo plazo la medicalización completa de la reproducción basada en la genetización podría ser una realidad. No obstante, el verdadero potencial de la genómica todavía nos resulta extraño. Muy pronto podremos cortar y pegar segmentos de ADN del embrión humano de forma muy sencilla. Sin embargo, llevará mucho más tiempo comprender completamente la genómica y las implicaciones epigenéticas de la genética reproductiva. Lo más destacable es que el ciclo de vida del ser humano es largo, y probar los beneficios de la genética reproductiva en la curación de las enfermedades multifactoriales de aparición tardía requerirá realizar un seguimiento a lo largo de la vida adulta de los bebés nacidos gracias a las técnicas de reproducción asistida. Por supuesto, mientras no se disponga de toda la información relevante, las fuerzas del mercado pueden inducir

especulaciones científicas, creencias y expectativas, con imaginarios socio-tecnológicos que se derivan de los beneficios percibidos de la genetización.

Este estudio concluye que, teniendo en cuenta que la medicalización de la reproducción es un proceso largo y fácilmente observable, la hipótesis de la genetización probablemente no se producirá de forma disruptiva (Brown & Michael, 2003), inserta en un proyecto de investigación particular de alguna institución o empresa. Alternativamente, tomará la forma de un proceso en forma de espiral, impulsado por los engranajes de las fuerzas del mercado, los intereses privados, las tendencias alimentadas por imaginarios socio-tecnológicos y por los cambios que se vayan produciendo en la regulación. Dicho proceso no será necesariamente bueno o malo, pero es recomendable monitorizarlo, intentar influir en su desarrollo y dirigirlo adecuadamente en beneficio de la sociedad, a través de una correcta regulación tanto a nivel nacional como internacional.

Los paneles de expertos mostraron repetidamente su preocupación por la gran influencia de los intereses comerciales en la regulación, en contraste con la débil influencia que parecen tener los intereses éticos y las consideraciones de salud. A pesar de las diferencias en la cuota de mercado que las empresas privadas representan en el ámbito de las TRA en los dos países analizados, una parte de la demanda está inducida, en ambos casos, por intereses privados. Nuestro análisis plantea que, a pesar de los grandes beneficios económicos que reporta la industria de TRA, los gobiernos deberían aspirar a ralentizar el proceso de medicalización.

En resumen, los reguladores deberían evitar el "sonambulismo" consistente en permitir un impulso tecnológico descontrolado (Nuffield Council on Bioethics, 2018). Por otra parte, nuestras consideraciones morales tampoco deberían basarse en contextos obsoletos o engañosos, que pueden conducir a expectativas exageradas o a teorías distópicas infundadas. A lo largo del proceso de medicalización de la reproducción se precisa de un debate abierto que aborde regularmente las cuestiones relacionadas con la libertad de elección y la autonomía personal en la toma de decisiones, y que además debe actualizarse periódicamente de acuerdo con el contexto científico más realista y preciso.

References:

Adner, R. (2004). A Demand-Based Perspective on Technology Life Cycles. In A. M. Joel A.C. Baum, Business Strategy over the Industry Lifecycle (Advances in Strategic Management, 21) (pp. 25-43, doi: 10.1016/S0742-3322(04)21001-4). Emerald Group Publishing Limited.

Agarwal, A., Mulgund1, A., Hamada, A., & Chyatte, M. R. (2015). A Unique View on Male Infertility Around the Globe. Reproductive Biology and Endocrinology, 13:37, doi 10.1186/s12958-015-0032-1.

Amir-Aslani, A., & Mangematin, V. (2010). The Future of Drug Discovery and Development: Shifting Emphasis Towards Personalized Medicine. Technological Forecasting & Social Change, 77, 2, 203-2017, doi: 10.1016/j.techfore.2009.09.005.

ASRM, P. C. (2015). Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility, 103(3): e18-25, doi: 10.1016/j.fertnstert.2014.12.103.

Barberá-Tomás, D., & Consoli, D. (2012). Whatever Works: Uncertainty and Technological Hybrids in Medical Innovation. Technological Forecasting and Social Change, 79, 5, 932-948 doi: org/10.1016/j.techfore.2011.12.009.

Beck-Gernsheim, E. (2000). Health and Responsibility: From Social Change to Technological Change and Vice Versa. In B. Adam, U. Beck, & J. Van Loon, The Risk Society and Beyond: Critical Issues for Social Theory (pp. 122-134). London: Sage.

Boivin, J., Bunting, L., A. Collins, J., & Nygren, K. G. (2007). International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. Human Reproduction, 22, 6, 1506–1512, doi: 10.1093/humrep/dem046.

Boon, W. P., Aardenb, E., & Broerse, J. E. (2015). Path creation by public agencies — The case of desirable futures of genomics. Technological Forecasting & Social Change, 99, 67–76, doi: 10.1016/j.techfore.2015.06.038.

Borup, M., Brown, N., Konrad, K., & Van Lente, H. (2006). The Sociology of Expectations in Science and Technology. Technology Analysis & Strategic Management, 18, 3/4, 285–298, doi: 10.1080=09537320600777002.

Brigham, K. B., Cadier, B., & Chevreul, K. (2013). The Diversity of Regulation and Public Financing of IVF in Europe and Its Impact on Utilization. Human Reproduction, 28(3), 666-75, doi: 10.1093/humrep/des418.

Brown, N., & Michael, M. (2003). A Sociology of Expectations: Retrospecting Prospects and Prospecting Retrospects. Technology Analysis & Strategic Management, 15:1, 3-18, doi: 10.1080/0953732032000046024.

Buchanan, A., Brock, D. W., Daniels, N., & Wikler, D. (2000). From Chance to Choice: Genetics and Justice. Cambridge University Press.

Casper, R. H., B., H. T., Bassil, R., & Mehta, C. (2017). Recent Advances in in Vitro Fertilization. F1000Research, F1000Research 2017, 6(F1000 Faculty Rev):1616 (doi: 10.12688/f1000research.11701.1).

CDC. (2018). Assisted Reproductive Technology - National Summary Report 2016. Atlanta, US: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, https://www.cdc.gov/art/pdf/2016-report/ART-2016-National-Summary-Report.pdf.

Chambers, G. M., Sullivan, E. A., Ishihara, O., Chapman, M. G., & Adamson, G. D. (2009). The Economic Impact of Assisted Reproductive Technology: A Review of Selected Developed Countries. Fertility and Sterility, 91(6), 2281-94, doi: 10.1016/j.fertnstert.2009.04.029.

Devaney, L., & Henchion, M. (2018). Who is a Delphi 'Expert'? Reflections on a Bioeconomy Expert Selection Procedure from Ireland. Futures, 99, 45–55, doi: org/10.1016/j.futures.2018.03.017.

Di Stefano, G., Gambardella, A., & Veronab, G. (2012). Technology Push and Demand-Pull Perspectives in Innovation Studies: Current Findings and Future Research Directions. Research Policy, 41(8), 1283-1295, doi: 10.1016/j.respol.2012.03.021.

Dosi, G. (1982). Technological Paradigms and Technological Trajectories: A Suggested Interpretation of the Determinants and Directions of Technical Change. Research Policy, 11(3): 147-162, doi: 10.1016/0048-7333(82)90016-6.

ESHRE. (2018). Assisted Reproductive Technology in Europe, 2014: Results Generated from European Registers by ESHRE. Human Reproduction, 33, 9, 1586–1601, doi: 10.1093/humrep/dey242.

Evers, J. L. (2002). Female Subfertility. The Lancet, 13; 360(9327), 151-9, doi: 10.1016/S0140-6736(02)09417-5.

Fukuyama, F. (2002). Our Posthuman Future, Consequences of the Biotechnology Revolution. New York: Farrar, Straus and Giroux.

Godinho, M. M. (2016). Uma Brevíssima História do Futuro - Ensaio Sobre Como Limitar os Futuros Possíveis a Futuros Preferíveis. ISEG - Lisbon School of Economics and Management.

Greely, H. T. (2016). The End of Sex and the Future of Human Reproduction. Cambridge: Harvard University Press.

Griessler, E., & Hager, M. (2017). Changing Direction: The Struggle of Regulating Assisted Reproductive Technology in Austria. Reproductive Biomedicine online, 3, 68-76, doi: 10.1016/j.rbms.2016.12.005.

Habermas, J. (2003). The Future of Human Nature. Cambridge: The translation polity press.

Hammarberg, K., Kirkman, M., & de Lacey, S. (2016). Qualitative Research Methods: When to Use Them and How to Judge Them. Human Reproduction, 31, 3, 498–501, doi: 10.1093/humrep/dev334.

Harari, Y. N. (2011). Sapiens: A Brief History of Humankind. Jerusalem: Dvir.

Harari, Y. N. (2016). Homo Deus: A brief history of tomorrow. London: Harvill Secker.

Harris, J. (2007). Enhancing Evolution, The Ethical Case of Making Better People. New Jersey: Princeton University Press.

Hashiloni-Dolev, Y., & Raz, A. E. (2010). Between Social Hypocrisy and Social Responsibility: Professional Views of Eugenics, Disability and Repro-Genetics in Germany and Israel. New Genetics and Society, 29(1) 187–102, doi: 10.1080/14636770903561364.

Ho M., et al. (2016). A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies. Value in Health, 19) 6, 746-750.

Hofer, M. P., Jakobsson, C., Zafiropoulos, N., Vamvakas, S., Vetter, T., Regnstrom, J., & Hemmings, R. J. (2015). Regulatory Watch: impact of Scientific Advice From. The European Medicines Agency., 302-303, doi: 10.1038/nrd4621.

Inhorn, M. C., & Patrizio, P. (2015). Infertility Around the Globe: New Thinking on Gender, Reproductive Technologies and Global Movements in the 21st Century. Human Reproduction Update, 21, 4,.411–426, doi: 10.1093/humupd/dmv016.

Ishihara, O. e. (2019). Assisted reproductive technology in Japan: A summary report for 2016 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol., 18(1): 7–16, doi: 10.1002/rmb2.12258.

Jasanoff, S., & Metzler, I. (2018). Borderlands of Life: IVF Embryos and the Law in the United States, United Kingdom, and Germany. Science, Technology, & Human Values, 1-37, doi: 10.1177/0162243917753990.

Johnson, L. (2014). Regulation of Assisted Reproductive Treatment (ART) in Australia & Current Ethical Issues. Indian Journal of Medicine Research, 140(Suppl 1): S9–S12.

Johnson, M., & Petersen, K. (2008). Public Interest or Public Meddling? Towards a Subjective Framework for the Regulation of Assisted Reproduction Technologies. Human Reproduction, 23(3): 716-28, doi: 10.1093/humrep/dem387.

Krimsky, S. (2019). Ten Ways in Which He Jiankui Violated Ethics. Nature Biotechnology, 37, 19, doi.org/10.1038/nbt.4337.

Landeta, J. (2002). El Método Delphi, Una téecnica de previsión del futuro. Barcelona: Ariel.

Landeta, J., & Barrutia, J. (2011). People Consultation to Construct the Future: A Delphi Application. International Journal of Forecasting, 27(1), 134–151, doi: org/10.1016/j.ijforecast.2010.04.001.

Landeta, J., J., M., Ruíz, V., & Galter, J. (2008). Results of a Delphi Survey in Drawing Up the Input–Output Tables for Catalonia. Technological Forecasting & Social Change, 75(1), 32–56, doi: org/10.1016/j.techfore.2007.01.005.

Lewis, C. S. (1943). The Abolition of Man. New York: Oxford University Press.

Lippman, A. (1991). Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities. American Journal of Law and Medicine, 17(1-2):15-50.

Lu, L., Lv, B., Huang, K., Xue, Z., Zhu, X., & Fan, G. (2016). Recent Advances in Preimplantation Genetic Diagnosis and Screening. Journal of Assisted Reproduction and Genetics, 33, 9,1129–1134, doi: 10.1007/s10815-016-0750-0.

Marchant, G. E. (2011). The Growing Gap Between Emerging Technologies and the Law. In G. E. Marchant, B. R. Allenby, & J. R. Herkert, The Growing Gap Between Emerging Technologies and Legal-Ethical Oversight (pp. 19-33). Dordrecht: Springer.

Martin, L. J. (2014). The World's Not Ready for This: Globalizing Selective Technologies. Science, Technology, & Human Values, 39(3), 432-455, doi: 10.1177/0162243913516014.

Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS Medicine, 9(12): e1001356. doi: 10.1371/journal.pmed.1001356.

Mayor, B., Casada, R. R., L. J., López-Gunn, E., & Villarroya, F. (2016). An Expert Outlook on Water Security and Water for Energy Trends to 2030–2050. Water Policy, 18 (1) 1-18; doi: 10.2166/wp.2015.196.

Melander, L. (2018). Scenario Development in Transport Studies: Methodological Considerations and Reflections on Delphi Studies. Futures, 96, 68–78, doi: org/10.1016/j.futures.2017.11.007.

Murphy, T. (2014). In Defense of Prenatal Genetic Interventions. Bioethics, 28(7), 335-42, doi: 10.1111/j.1467-8519.2012.02009.x.

Nelson, E. L. (2006). Comparative Perspectives on the Regulation of Assisted Reproductive Technologies in the United Kingdom and Canada. Alberta Law Review, 43, 4, 1023-1048, doi: org/10.29173/alr398.

Nemet, G. F. (2009). Demand-Pull, Technology-Push, and Government-Led Incentives for Non-Incremental Technical Change. Research Policy, 38(5) 700–709, doi: 10.1016/j.respol.2009.01.004.

Nuffield Council on Bioethics. (2018). Genome Editing and Human Reproduction: Social and Ethical Issues. London.

Okoli, C., & Pawlowski, S. D. (2004). The Delphi Method as a Research Tool: An Example, Design Considerations and Applications. Information & Management, 42(1), 15–29, doi: 10.1016/j.im.2003.11.002.

Paraskevopoulou, E. (2012). Non-Technological Regulatory Effects: Implications for Innovation and Innovation Policy. Research Policy, 41,6, 1058– 1071, doi: org/10.1016/j.respol.2012.03.018.

Paunov, C. (2013). Innovation and Inclusive Development: A Discussion of the Main Policy Issues. OECD Science, Technology and Industry Working Papers 2013/1, doi: org/10.1787/18151965.

Pavone, V., & Arias, F. (2012). Beyond the Geneticization Thesis: The Political Economy of PGD/PGS in Spain. Science, Technology, & Human Values, 37(3) 235-261, doi: 10.1177/0162243911411195.

Pennings, G., de Mouzon, J., Shenfield, F., & Ferraretti, A. P. (2014). Socio-Demographic and Fertility-Related Characteristics and Motivations of Oocyte Donors in Eleven European Countries. Human Reproduction, 5, 1076–1089, doi: 10.1093/humrep/deu048.

Peters, M., Schneider, M., Griesshaber, T., & Hoffmann, V. H. (2012). The Impact of Technology-Push and Demand-Pull Policies on Technical Change – Does the Locus of Policies Matter? Research Policy, 41(8), 1296-1380, doi: org/10.1016/j.respol.2012.02.004.

Präg, P., & Mills, M. C. (2017). Assisted Reproductive Technology in Europe: Usage and Regulation in the Context of Cross-Border Reproductive Care. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 289-309). Berlin: Springer.

Ramsey, P. (1972). Shell we "Reproduce"? JAMA, 220 (10), 1346-1350; (11), 1481-1485.

Rawls, J. (1993). Political Liberalism. New York: Columbia University Press.

Rogers, E. M. (1983). Diffusion of Innovation, Third Edition. New York: The Free Press.

Sandel, M. J. (2004). The Case Against Perfection. The Atlantic, 293, 3, 51-62.

Savulescu, J. (2001). Procreative Beneficence: Why We Should Select the Best Children? Bioethics, 15(5-6), 413-26, doi: 10.1111/1467-8519.00251.

SEF. (2016). Registro Nacional de Actividad - Técnicas de Reproducción Asistida, Informe estadístico de Técnicas de Reproducción Asistida 2016.
https://www.registrosef.com/public/docs/sef2016_IAFIVm.pdf: Sociedad Española de Fertilidad.

Shulman, C., & Bostrom, N. (2014). Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer? Global Policy, 5(1) 85-92, doi: 10.1111/1758-5899.12123.

Silver, M. L. (1997). Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family. New York: Harper Perennial.

Sobotka, T. (2016). Childlessness in Europe: Reconstructing Long-Term Trends Among Women Born in 1900–1972. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 17-50). Berlin: Springer Open.

Spar, L. D. (2006). The Baby Business, How Money Science, and Politics Drive the Commerce of Conception. Boston, Massachusetts: Harvard Business School Press.

Teece, D. J. (1986). Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy. Research Policy, 15(6), 285-305, doi: 10.1016/0048-7333(86)90027-2.

Von der Gracht, H. A. (2012). Consensus Measurement in Delphi Studies Review and Implications for Future Quality Assurance. Technological Forecasting & Social Change, 79(8), 1525–1536, doi: 10.1016/j.techfore.2012.04.013.

Walsh, V. (1983). Invention and Innovation in the Chemical Industry: Demand-Pull or Discovery-Push? Research Policy, 13(4) 211-234, doi: 10.1016/0048-7333(84)90015-5.

Zlotogora, J. (2014). Genetics and Genomic Medicine in Israel. Molecular Genetics & Genomic Medicine, 2(2): 85–94, doi: 10.1002/mgg3.73.

Zuckerman, S., Zeevi, D. A., Gooldin, S., & Altarescu, G. (2017). Acceptable Applications of Preimplantation Genetic Diagnosis (PGD) among Israeli PGD Users. European Journal of Human Genetics, 25, 1113–1117, Doi: 10.1038/ejhg.2017.113.

2. WHAT TO EXPECT FROM ASSISTED REPRODUCTIVE TECHNOLOGIES? EXPERTS' FORECASTS FOR THE NEXT TWO DECADES

2.1. Introduction

Assisted Reproductive Technologies (ART) are medical procedures that facilitate human reproduction through the manipulation of both oocytes and sperm, and their fertilization under laboratory conditions (CDC, 2018). The most commonly used ART is In-Vitro Fertilization (IVF), which also enables reproductive genetics through embryo selection or engineering. In recent decades, the use of IVF has proliferated, and it is already standing behind a considerable share of human reproduction and producing a growing impact on human society. In Europe 7,623 IVF cycles per million women aged 15-45 were reported in 2014, compared with only 879 IVF cycles in 2007 (ESHRE, 2012, 2018).

In some leading countries, IVF births already exceed 5% of the total, such as in Japan, Spain, Denmark, Greece, Austria, Czech Republic and Slovenia (SEF, 2016; ESHRE, 2018; Ishihara et al., 2019). Also, preimplantation genetic testing (diagnosis and screening), has gained popularity and in 2016 accounted for 22% of IVF cycles in the U.S. (CDC, 2018). Most recently, genetic engineering of embryos by CRISPR/Cas has caught the world's attention with the announcement of the first birth of genetically edited babies in China in December 2018 (Krimsky, Ten Ways in Which He Jiankui Violated Ethics, 2019).

Medical technology is marked by many as one of most promising S&T areas in the 21st century, where increasing innovative efforts promise to extend human life and improve human happiness (Amir-Aslani & Mangematin, 2010; Harari, 2016; Godinho, 2016). In this context, ART is raising high expectations by enabling the extension of reproductive age and through the introduction of reproductive genetics, which could allow preventing diseases from the outset and even enhancing the human race.

ART is already subject to greater regulations compared with other medical sectors (Brigham et al., 2013), and emerging social and ethical issues pose growing challenges (Johnson, 2014). Establishing appropriate regulatory policies requires better understanding and anticipation of the innovation trajectories of ART (Boon et al., 2015).

This work broadly focuses on the diffusion of ART as an innovation. Diffusion is "the process by which an innovation is communicated through certain channels over time among the members of a

social system" (Rogers, 1983, p. 12). There are different supply and demand-side factors influencing the diffusion of innovation, since technological trajectories are always shaped not only by scientific advances but also by economic, social and institutional factors (Dosi, 1982). Indeed, the literature on technological change emphasizes that the process of innovation is not linear but interactive, as the technology and its users affect each other along the way (Walsh, 1983; Peters et al., 2012; Di Stefano et al., 2012).

On the supply side, technological progress provides more solutions to infertility with higher success rates of ART at lower costs. On the demand side, infertility is growing due to the steady advance in parenting age (Kovac et al., 2013; Johnson, 2014; Mathews & Hamilton, 2016; OECD, 2018), environmental hazards and unhealthy lifestyles (Mascarenhas et al., 2012; Majumdar & Tiwari, 2014). ART also offers new possibilities of parenting for singles and same-sex couples, and at later stages through fertility preservation (Machado & Galdeano, 2011; Lemoine & Ravitsky, 2015).

The academic discussion around ART has largely focused on issues of good medical practice associated with the health of patients and infants (Chambers et al., 2014; ESHRE, 2014), followed by ethical-legal dilemmas and different social risks and opportunities (Ravitsky, 2012; Wilkinson, 2015). The latter range from worries of excessive medicalization (geneticization) of reproduction, with the threats of a new eugenic era (Buchanan et al., 2000; Habermas, 2003; Wailoo & Pemberton, 2006; Christensen et al., 2015), to optimistic expectations for human enhancement and fertility control (Savulescu, 2001; Harris, 2011)

However, those risks and opportunities can be considered purely speculative if they are not grounded in a likely future. To the best of our knowledge, there is no well-founded research about the expected development of ART that could help to distinguish realistic scenarios from unrealistic ones. Indeed, there appears to be a knowledge gap between physicians, academic scholars, and the civil society, both regarding the viability and the timing of upcoming innovations in ART. This gap is associated with the complexity of medical procedures and the speed of technological progress (Marchant, 2011). Reducing such gap is particularly important considering the role of regulations at the current developmental stage of ART.

In order to contribute to this agenda, we conducted a technology forecasting study by applying the Delphi method on a panel of experts, combined with in-depth interviews. Our study captures and disseminates the knowledge and expectations of 25 leading gynecologists and geneticists from two relevant countries, Israel and Spain, enabling to assess possible scenarios regarding developments and future practices of IVF and preimplantation genetic testing (diagnosis and screening). We expect our findings to allow a better understanding of innovation trajectories in ART (Boon et al., 2015; Harmon,

2016), which may guide not only policy response but also technology developers and users (Palm & Hansson, 2006). It may also contribute to detecting those social and ethical issues that will likely pose growing challenges to regulators.

2.2. Background

In this section, we set the ground for examining technological trajectories and demand trends in ART. We begin by introducing some technical details of IVF and reproductive genetics and continue by discussing different views regarding the social implications of the medicalization of reproduction (the geneticization thesis).

2.2.1. In-vitro fertilization

Infertility affects from 10 to 15 percent of couples worldwide (ASRM, 2015; Agarwal et al., 2015). The causing etiologies significantly differ from place to place and time to time, including age, environmental, infectious, genetic and dietary factors (Mascarenhas et al. 2012). The most common female factor for cycles of ART in the U.S. (2016) was diminished ovarian reserve (31%), which is strongly related to women's advanced age (Cai et al., 2011; CDC, 2018). Meanwhile, 32% of ART cycles were performed due to male factor dysfunctions, such as low concentration and quality of spermatozoa, which may be caused by age, environmental, genetic and life-style factors (Kovac et al., 2013; ASRM, 2015; CDC, 2018).

Conventional IVF has been practiced since 1978. It consists of placing oocytes in semen for fertilization to take place in a controlled environment. Its success depends on the quantity and quality of available gametes, as well as on the methods of fertilization, incubation and laboratory conditions, which are improving substantially (Cai et al., 2011; Casper et al., 2017). If the number of spermatozoa required for in vitro insemination is not available, intra-cytoplasmic sperm injection (ICSI), which was introduced in 1991, could be used. ICSI entails picking up one spermatozoon, selected according to its morphology, and injecting it directly into the cytoplasm (Palermo et al., 2009).

ICSI is more invasive than conventional IVF and disables more strongly the functions of natural selection, which has been raising concerns regarding health implications, particularly in the long-term (Fauser et al., 2014; ESHRE, 2014). Although it is yet to be proven entirely safe, 66% of ART cycles in the U.S. and the majority of cycles in Europe are done by ICSI nowadays (ESHRE, 2018; CDC, 2018), due to its higher efficiency. In this article, we use the term IVF to refer to both methods.

Another critical technological component of IVF is controlled ovarian hyperstimulation by gonadotropins. It enables the ovaries to produce more oocytes, which can be extracted by oocytes

retrieval (OCR) and fertilized to a larger number of embryos, remarkably increasing the prospects of an IVF cycle (Cai et al., 2011). Overall, it is the longest and most unpleasant stage of IVF, which bears health risks to the patient due to the use of hormones, the invasiveness and the anesthesia (Fauser et al., 2010; Aragona et al., 2011; Orvieto, 2013; La Marca & Sunkara, 2014).

In recent years, cryopreservation of gametes and embryos, performed by placing the cells in liquid nitrogen, has been a game-changer in ART. One important aspect is the vitrification of oocytes, which seems to result in outcomes comparable to those achieved with fresh oocytes and which enables the dislocation of donor-eggs and embryos (Cobo et al., 2013; SEF, 2016; Inhorn et al., 2017). It also opens the way for fertility preservation both for medical and non-medical reasons (Dondorp et al., 2012; Bhatia & Campo-Engelstein, 2018).

2.2.2. Genetic selection and enhancement

Preimplantation Genetic Diagnosis (PGD), introduced in 1990, is typically practiced to prevent the birth of infants with severe disorders, usually monogenic, of early onset, and of a high level of penetrance (Klitzman, 2008; Batzer & Ravitsky, 2009). However, it is also occasionally used for severe diseases of late onset and partial penetrance, such as neurodegenerative disorders and genetic malignancy risks (Altarescu et al., 2015).

PGD is performed by taking a biopsy from an embryo (3-5 days) and diagnosing it for pre-identified mutations (Milachich, 2014). In most cases, it may require an extensive pre-study of family members to identify a mutation (Altarescu et al., 2015). PGD is a labor-intensive procedure (Wang, 2014), customized for each family (Swanson et al., 2007).

Preimplantation Genetic Screening (PGS) also serves for embryo selection. However, instead of detecting gene mutations, screening serves as a global quantitative analysis of the entire genome with the aim to transfer only euploid embryos to increase the prospect of treatment. It is assumed that an euploid embryo without chromosomal structure anomalies has better chances to develop into a fetus and be born as a healthy baby (Lu et al., 2016; Casper et al., 2017). Despite its potential advantages, critics of PGS have claimed that abnormalities may be naturally fixed during the development of a fetus and that it causes the waste of good embryos due to a “false-positive” risk (Orvieto & Gleicher, 2016). Currently, prospective randomized control trials have shown only a modest advantage for employing PGS, and only for shortening the time to pregnancy in good prognosis patients who might need this technology (SART & ASRM, 2008; Orvieto, 2016).

The latest form of genetic intervention is provided by CRISPR-Cas, discovered in 2012, a promising technology of genetic engineering (GE), serving for gene-editing by allowing the replacement of DNA

segments. In July 2017 a team from Oregon Health and Science University reported a successful CRISPR/CAS editing of dozens of embryos which were not implanted (Ledford, 2017), as it is banned, in most countries, to implant a genetically modified human embryo into the uterus (Knoepfler, 2016). Nevertheless, while this technology is being developed, tested and debated around the world, the birth of the first genetically edited babies was announced by a biomedical researcher from Shenzhen, China, in December 2018.

2.2.3. Social controversies

Many controversies around these technological developments remain unresolved. On the one hand, ethical-philosophical discussions stem from concerns that expanded PGD (Regalado, 2017) will allow to select embryos, increase the geneticization of reproduction (Lippman, Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities, 1991), enable human enhancement or even the breeding of man (Lewis, 1947; Ramsey, 1972; Jonas, 1984; Buchanan et al., 2000). On the other hand, more confident proponents of ART have suggested that selecting healthier people would reduce the burden of health cost on individuals and society (Knoepfler, 2016), empower descendants with traits which evolution might bring only slowly if at all (Savulescu, 2001), and could be used to adjust and even reform humans (Mewes, 2002).

In order to provide the ground for a broad selection based on expanded PGD, many embryos would be required, and more than one “perfect” embryo must be detected to guaranty a live-birth (Nuffield Council on Bioethics, 2018). However, oocytes are scarce. Greely (2016) argues that the possibility to create gametes from stem cells would allow producing a large number of embryos for each patient enabling multi-factorial PGD. Other authors have gone further, suggesting that stem cells-derived gametes, combined with in-vitro maturation of oocytes, would enable to create multiple human generations inside a lab, resulting in rapid enhancement by selective breeding based on cognitive genomics (Shulman & Bostrom, 2014).

Ethical considerations expressed by regulations around the world also play an important role as ethicists intend to distinguish worthwhile-life from life-not-worth-living, in order to shape the limits of selection (Buchanan et al., 2000). Some of them stress the importance of human diversity and the loss for society due to the exclusion of individuals with disabilities who might hold advantageous characteristics (Koch, 2001; Garland-Thomson, 2015). Others defend children’s right to autonomy and an open future, which could be disturbed by excessive selection based on parents’ desires (Jonas, 1984; Habermas, 2003).

In a future perspective, a common preoccupation is that the significant advantages given to a genetically selected person, alongside with inequality in access to ART, may raise inequality in terms

of employment and eligibility to insurance. (Buchanan et al., 2000; Wailoo & Pemberton, 2006). Fukuyama (2002) stresses that such a "posthuman" world could be far more hierarchical and fuller of social conflicts. Ultimately, reproductive genetics is often accused of inducing eugenics, i.e. the desire to enhance society with stronger, smarter and "better" people (Garland-Thomson, 2015), leading to the question of what exactly is "better" and who should deliver such judgment (Hubbard, 1993; Knoepfler, 2016).

Nevertheless, as of today, PGD has been a marginal technology, used for a very limited amount of severe genetic disorders, and it is unclear whether it may in the future provide benefit to a larger portion of the population and become a popular medical technology, given the vast amount of additional unknown and unpredicted factors of genetic or epigenetic origin. However, as it is often the case with other technologies, incremental innovation, unexpected trajectories and new "varieties of application" play an important role in shaping the diffusion of innovation (Rip & Schot, 2002). In the following sections, we attempt to introduce possible scenarios to the diffusion course of ART, based on the forecast of 25 experts from Israel and Spain.

2.3. Method

We used the Delphi method to anticipate the evolution of ART, a widely used approach in technological forecasting. Delphi studies build on a panel of experts who contribute with their knowledge and experience to reach a consensus or build common scenarios (Okoli & Pawlowski, 2004; Melander, 2018). Despite being a qualitative method, it is based upon a quantitative survey in an anonymous and interactive process. The experts must be consulted at least twice to allow them changing their replies or add comments after learning the general views (Von der Gracht, 2012; Mayor et al., 2016). We combined the Delphi survey (which was launched in 2017) with a set of previous in-depth personal interviews addressed to well-known and highly recognized ART physicians. These interviews guided the design of the Delphi questionnaire and helped to select the final sample of experts while enriching our analysis with deeper qualitative insights.

2.3.1. Sampling

Our selection of experts was primarily based on the criteria of practical experience in performing IVF and PGD, presuming that physicians who have practiced these technologies for long are being regularly updated with innovations in the field, and are in an optimal position to predict technological developments as well as forecast demand and regulations. These experts play an important role in a "user-centered innovation process" by interacting with equipment manufacturers and pharmaceutical industry, by sharing their experiences via publications, and sometimes by conducting innovations

themselves (Von Hippel, 2005; Chatterji et al., 2008). Health care professionals also influence how and when new medical technology is used (Toiviainen et al., 2003; Skirton et al., 2013).

We approached only IVF clinics that practice PGD, focusing on two countries where rates of ART are among the highest worldwide: Israel and Spain. In Israel, 20,600 IVF cycles per million women aged 15-49 were performed in 2016, the highest worldwide in relative terms mostly due to its very comprehensive public coverage. In 2016, 4.7% of births in Israel were assisted by IVF (Health Ministry of Israel, 2018). Spain is the largest provider of IVF in Europe and third in the world, with 138,553 IVF cycles in 2016 (SEF, 2016), following a sharp growth in the last decade. In 2016, 8% of total births in Spain were assisted by IVF (SEF, 2016).

According to the European Society of Human Reproduction and Embryology (ESHRE, 2018), as much as 36% of PGD/PGS procedures in Europe in 2014 were performed in Spain, among other factors because of the country's permissive attitudes towards PGD/PGS relative to other European countries (Pavone & Arias, Beyond the Geneticization Thesis: The Political Economy of PGD/PGS in Spain, 2012). Furthermore, in 2016, 3.8% of live births from IVF in Spain involved the use of PGD/PGS (SEF, 2016). Although there are no official statistics, we estimate a high percentage of PGD/PGS in Israel due to venturesome practices of PGD procedures, extensive coverage by public health insurance (Zlotogora, 2014), and the frequent use of PGS for patients of advanced age. It is also a result of a very liberal approach towards ART with a tendency to "quest for the perfect baby" by preventing births of disabled fetuses (Zuckerman et al., 2017).

We approached over 50 experts from these two countries and obtained the voluntary participation of 25 senior gynecologists and geneticists who formed the final group, a panel size within the recommended range for Delphi studies (Landeta, 2002). The panel counted 13 experts from Spain and 12 from Israel, 8 women and 17 men, with an average of 19 years of experience in the field.

A substantial difference between experts from the two countries should be noted. Among twelve Israelis, nine worked in public hospitals and only three in clinics of a mixed character. The expert's selection in Israel was straightforward, as there were only eight PGD laboratories, six of them located in the largest public hospitals. Conversely, in Spain, there were many more PGD laboratories, and among the thirteen Spanish participants only three worked in public hospitals, while the rest in private clinics. Our focus in Spain was on the largest network of IVF clinics, which also facilitated the data collection thanks to the snowball effect (Ribeiro & Quintanilla, 2015).

2.3.2. Data collection

Seventeen semi-structured interviews lasting one hour on average were conducted aiming to form the Delphi questionnaire with the assistance of some selected experts, and to gather additional qualitative insights. The interviewees were IVF department/clinic directors, PGD laboratory directors and senior doctors and geneticists in elite IVF+PGD clinics. Most of the interviewees participated as well in the subsequent Delphi survey, and many of them recommended other experts, creating a "snowball" effect (Ribeiro & Quintanilla, 2015).

We approached the interviews using a draft questionnaire based on an exhaustive literature review. Each interview led to the deletion of irrelevant questions, to the reframing of some, and occasionally to add others. The interviews lasted until we felt that additional interviewees were only providing marginal suggestions for change. The final Delphi questionnaire was tested during the last three interviews and reviewed by an internationally recognized expert in the Delphi method.

The questionnaire referred to a 20 years' horizon, as recommended by the experts. It was composed of three sections, the first two mostly based on 10-point scale questions. Firstly, the IVF section evaluated the potential impact of different technologies. The second section dealt with different categories of genomics and focused on experts' expectations regarding expanded PGD and genetic engineering. Finally, the last section included quantitative estimates and ranking answers to evaluate experts' perceptions concerning future demand and its explanatory factors. We left an open space for comments in each question.

The first Delphi round was conducted using an online survey platform. In the second round, we highlighted the answers for each expert which significantly differed from the central tendency of the first round and asked each of them regarding inconsistencies or strong deviation from the group. We focused the second round on question in which consensus was not achieved in the first round (Skirton et al., 2013). Participants were offered the option to change their replies or add open comments to explain their skewed position (Okoli & Pawlowski, 2004; Von der Gracht, 2012).

Due to the experts' restricted availability, the Delphi was limited to two rounds regardless of the degree of consensus achieved, a practice which is methodologically sound (Landeta, 2002; Von der Gracht, 2012). Moreover, we preferred to receive experts' comments explaining their divergent replies rather than pushing them to converge into consensus by repeating the process exhaustively (Dayé, 2018). Out of 25 participants, 6 did not reply to the second round, and their replies from the first round were kept as definitive, which is considered a valid practice within the Delphi method (Landeta et al., 2011; Mayor et al., 2016).

2.3.3. Statistical analysis

The analysis was mainly based on descriptive statistics focusing on central tendency and dispersion, as usual in Delphi studies (Von der Gracht, 2012). In questions using a 10-point scale and quantitative estimates, an average of all categories was calculated to facilitate the comparison between questions as well as the analysis of correlations. The level of consensus among participants was measured by the standard deviation (SD), considering (SD<2) as a reasonable consensus.

We used the non-parametric Mann–Whitney U test for two independent groups to identify subgroups, and the Wilcoxon signed-rank test (2-related samples) to define differences between categories and between the averages. In all tests, we considered a 0.05 significance level and calculated the estimated effect-size[1] by the formula: $r = Z/(\sqrt{N})$ to measure the magnitudes of our findings (Field, 2009; Fritz & Morris, 2012). We also tested for Spearman correlations between different questions and experts' characteristics, to assess the consistency of the replies and to verify the existence of subgroups (Landeta et al., 2008).

Following a comparative analysis of both groups of experts, we found 6 questions (out of 63) where answers significantly differed by country, four of them concerning the same category (section 4.1). In view of these differences, we present the results of both panels separately.

2.4. Results

2.4.1. In-vitro fertilization

The main results from the first part of the questionnaire are shown in Table 1. In questions Q1, Q2 and Q3, we asked for the potential impacts, within the following 20 years, of different technology categories in three sequential stages of IVF: oocytes retrieval, oocytes fecundation, and embryo implantation. In order to assess how each IVF stage impacts its subsequent stage, Q2 included a category summarizing all categories of Q1, and similarly, Q3 included a category summarizing all categories of Q2 (marked by parentheses). This approach also enabled to verify the consistency of the replies, as answers for these two categories were correlated with their respective question average. In the last question of this section (Q4), a chart was presented to the respondents with birth rates per IVF cycle for women younger than 35 years, in the two countries (rates rose from around 23% in 2011 to around 25% in 2014), asking them to provide their forecasts.

[1] r=0.10, r=0.30, r=0.50 (in absolute values) represent small, medium and large effect sizes respectively.

Table 1. IVF - Potential impacts of different technology categories

	Israel (n=12)		Spain (n=13)		Mann-Whitney test		
Q1. Oocytes Retrieval**	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
Accumulation of oocyte by cryopreservation	6.8	2.05	8.1	1.38	48	p=0.096	r=-0.333
Ovarian tissue cryopreservation at a young age	5.9	2.91	5.8	2.51	65.5	p=0.725	r=-0.072
Mitochondrial Manipulation Technologie (MMT)	5.5	2.16	5.4	2.26	69.5	p=0.905	r=-0.024
Oocytes from stem cells	5.1	3.18	6.1	3.01	61	p=0.538	r=-0.126
In-Vitro Maturation (IVM)	4.9	2.54	5.2	2.01	71	p=0.700	r=-0.077
Improved controlled ovarian hyperstimulation and Oocyte Retrieval (OCR) methods	3.7	2.06	4.5	1.76	58.5	p=0.276	r=-0.218
IVF augment – supplementation by mitochondria from oocytes	4.4	3.01	3.8	1.77	71	p=0.977	r=-0.006
Average Q1	5.2	1.79	5.6	0.88	62.5	p=0.399	r=-0.169
Q2. Oocytes Fecundation**	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
Advanced incubators and temperature regulation – Optimal embryo culture environment	6.3	2.30	7.7	1.60	51.5	p=0.143	r=-0.293
Improved clinic quality control and conditions	5.7	1.97	7.2	1.52	43	p=0.053	r=-0.387
Quality improvement and quantity increase of oocytes (Q1)	5.3	2.49	7.2	2.24	42.5	p=0.052	r=-0.389
Improved methods for sperm selection	5.4	2.42	6.3	1.49	56.5	p=0.377	r=-0.180
Robotic technologies	4.8	2.64	6.8	2.01	41.5	p=0.079	r=-0.358
Improved fertilization methods	4.1	2.19	6.3	1.32	30.5	**p=0.008**	r=-0.528
Sperm-enhancement	3.9	2.08	6.1	1.44	27	**p=0.016**	r=-0.500
Average Q2	5.1	1.95	6.8	1.05	40.5	**p=0.041**	r=-0.409
Q3. Embryos Implantation**	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
Improved Preimplantation Genetic Screening (PGS)	6.4	2.87	8.4	1.19	50	p=0.121	r=-0.310
Quality improvement and quantity increase of embryos (Q2)	6.4	1.78	7.8	1.77	36.5	**p=0.021**	r=-0.460
Artificial Intelligence (classification models) - to identify the best embryos	6.5	2.39	7.3	1.49	67.5	p=0.561	r=-0.116
Advanced incubators and temperature regulation – optimal embryo culture environment	6.3	1.92	7.2	1.69	60	p=0.317	r=-0.200
Improved clinic quality control and conditions	6.2	2.04	7.1	1.61	58.5	p=0.281	r=-0.216
Improved methods of transplantation – timing and location	5.5	2.02	6.6	2.18	57.5	p=0.260	r=-0.225

Robotic technologies	5.1	2.02	6.5	2.03	53.5	p=0.174	r=-0.272
Average Q3	6.1	1.59	7.3	1.19	44	p=0.064	r=-0.371
Q4. Birth rates per IVF cycle for patients younger than 35 years	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
In the next 10 years	32.1%	4.50	43.6%	11.3	36.5	**p=0.036**	r=-0.429
In the next 20 years	42.1%	8.65	54.0%	14.3	46.5	p=0.130	r=-0.309

* Significant p-values are marked in bold.
** From 1–no impact to 10-very high impact

In this section, the Spanish panel reached high levels of consensus in most questions, as measured by the standard deviation, and in general higher levels than the Israeli panel which had a mild consensus. The level of consensus achieved in the second round was higher than in the first one for 70% of the questions. Overall, both panels identified the highest potential impact on technologies related to embryo selection and implantation. The Spanish panel attributed the second highest potential to oocytes fecundation and was least optimistic regarding improvements in oocytes retrieval. For the Israeli panel, there were no significant differences between the mean reply to Q1 (Oocyte retrieval) and Q2 (Oocytes Fecundation), according to the Wilcoxon test (p=0.859, r=-0.036). Generally, in the IVF section there were significant differences between the Israeli panel and the Spanish panel, implying that the latter was more optimistic regarding the impact of some technologies and the improvement of IVF birth rates. According to the Mann-Whitney tests, these differences were statistically significant in four categories, and for the average of Q2 (Oocytes Fecundation), as reported in Table 1.

Concerning the first stage of IVF (oocyte retrieval), both panels assigned the highest potential to cryopreservation for oocytes accumulation. Cryopreservation of ovarian tissues at a young age was also ranked among the most promising techniques. Available data confirm that oocyte cryopreservation already provides improvements in current IVF results, particularly when donor-eggs are used (SEF, 2016).

A lower consensus was observed regarding oocytes from stem cells. Some experts claimed that this procedure was already done in mice and could soon be practiced in humans, but many expressed concerns about epigenetic changes, with one expert stating that: "*it will require the use of a living ovary model in order to grow laboratory derived egg precursors; we are very far from being able to do that*". Likewise, while some experts were optimistic regarding In-Vitro maturation (IVM), the majority were pessimistic due to unsuccessful attempts to use IVM in recent years, and interviewees raised concerns regarding possible epigenetic impacts.

Concerning the second stage of IVF (oocytes fecundation), the most remarkable improvements were expected regarding incubation and clinic quality control. Interviews and comments suggested that in these categories there were some differences between the clinics under study. The results, as well as qualitative insights from Interviews and comments, suggest that the experts in both panels expect fewer radical innovations in this second stage, although they anticipate that average-budget laboratories will tend to catch up with the luxurious ones in terms of equipment, resulting in better laboratory conditions. This fact may also contribute to explain the differences between the panels from Israel (with most experts working in public clinics) and Spain (where most of them work for the private sector).

Lastly, in the stage of embryos implantation, the category PGS has attributed the highest impact. Four Israeli experts were skeptic regarding PGS (marked less than 5), some of whom considered it as a fraud, blaming it for causing a waste of good embryos, which could develop properly despite being abnormal at an early stage. However, most believed that PGS would improve enough to be added to a growing number of IVF cycles in the future. As explained by one interviewee: "*the focus of PGS should be genes and embryo's metabolism, i.e., shorter DNA sections rather than whole chromosomes. Accumulated experience is enabling geneticists to do so*". The panels also ranked highly the category "*classification models with artificial intelligence*" and, similarly to Q2, they attributed great potential to incubation and clinic quality control.

Testing for both panels simultaneously, experts with more years of experience seemed to be reasonably more optimistic regarding technological developments (Spearman correlation between years of experience and average Q1=0.398 (p=0.049), 0.492 for average Q2 (p=0.013) and 0.352 for average Q3 (p=0.084)). A statement from a senior Israeli doctor suggests that experts who witnessed far-reaching technological developments might recognize greater potential than their less experienced colleagues: "*if someone had told me 30 years ago about the technological methods I would be using today, I would have dismissed him as an unrealistic dreamer*".

Finally, in Q4 the Israeli panel predicted, on average, 32.1% live birth rates per IVF cycle in the next 10 years and 42.1% in the next 20 years, while the Spanish panel was more optimistic, and predicted 43.6% and 54%, respectively. Lack of consensus between the panels is also marked by the fact that, out of six experts who predicted less than 40% within 20 years, five were Israelis. A Spanish doctor suggested that "*national figures will tend to gradually reach 50% as already achieved currently by 'Premium IVF centers'*", an argument which was also echoed in other interviews.

2.4.2. Genetic selection and enhancement

Table 2 shows the experts' views regarding genomics (Q5), genetic engineering (GE) (Q6) and the viability of conducting an expanded PGD in terms of the number of available oocytes (Q7). We also collected the experts' views concerning the future of regulation of PGD and GE (Q8), and regarding potential advantages of a "*genetically selected person*" (Q9), shown in Tables 3 and 4 respectively.

Table 2. Genomics, genetic engineering and expanded PGD

	Israel (n=12)		**Spain (n=13)**		**Mann-Whitney test**		
Genomics (Q5)**	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
Neurological disorders	7.9	2.02	7.9	1.04	65.5	p=0.477	r=-0.142
Cancerous diseases	7.9	1.93	7.8	1.92	77.5	p=0.977	r=-0.006
Cardiovascular diseases	7.5	1.88	7.0	1.22	45	p=0.061	r=-0.374
Eyes/skin/hair color	6.8	2.17	6.1	2.02	50.5	p=0.129	r=-0.304
Physical traits	6.3	1.96	5.8	1.52	53.5	p=0.175	r=-0.271
Cognitive traits	5.3	2.30	4.9	2.06	59.5	p=0.309	r=-0.203
Average Q5	6.9	1.75	6.6	0.97	48.5	p=0.107	r=-0.322
Genetic Engineering (Q6)***	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
Gene replacements	7.3	2.71	8.0	1.35	77.5	p=0.977	r=-0.006
Fixing parts of chromosomes	6.3	3.06	5.7	2.59	56.5	p=0.239	r=-0.235
Remove multifactorial genetic disorders	5.5	2.75	5.7	2.46	73.5	p=0.805	r=-0.049
Physical Traits	4.7	2.81	3.8	1.95	66.5	p=0.527	r=-0.127
Cognitive enhancement	4.1	2.54	3.9	1.75	77	p=0.956	r=-0.011
Average Q6	5.6	2.55	5.4	1.48	69.5	p=0.643	r=-0.093
Embryos for expanded PGD (Q7)***	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect Size**
50 embryos or more	4.9	2.73	4.3	2.54	57.5	p=0.261	r=-0.225
100 embryos or more	3.1	1.34	2.7	1.59	55	p=0.198	r=-0.257
150 embryos or more	1.8	0.97	1.6	1.12	73	p=0.763	r=-0.060

* Significant p-values are marked in bold.
** From 1-no progress to 10-very high progress
*** From 1-not probable to 10-extremely probable

The experts were very optimistic, with consensus between the two panels, regarding improvements in genomics over the next 20 years. More specifically, they showed confidence in the ability to identify correlations between genes and different disorders and characteristics. Considering both panels jointly, results from Wilcoxon signed-rank tests showed that expectations regarding genomics were higher for both cancerous diseases and neurological disorders, each in comparison with cardiovascular diseases (p=0.019, r=-0.654; p=0.001, r=-0.468, respectively). Moreover, the

experts were slightly optimistic about the genomics of eyes, hair and skin color, as well as of physical traits, but less so regarding cognitive traits ($p=0.007$, $r=-0.542$ for color vs. cognitive traits, $p=0.012$, $r=-0.504$ for physical traits vs. cognitive traits, and $p=0.077$, $r=-0.354$ for color vs. physical traits, according to Wilcoxon tests for the joint results).

Additionally, the experts expected gene replacement by CRISPR/CAS to be available and safe within 20 years, with reasonable levels of consensus between both panels. They also estimated a high probability that GE would enable "*fixing parts of chromosomes*" and "*removal of multifactorial genetic disorders*".

Question Q7 was inspired from interviews, as several doctors confirmed that in order to perform a PGD for several mutations at once, many embryos would be required. One expert added that "*each person has on average 64 mutations that could be interpreted as causing disorders*". Though, some interviewees said that "*most people do not suffer severe diseases before an old age*" and one expert stated that by conducting an expanded PGD with prioritization of examined factors per each patient, "*few embryos will be found free from carrying severe disorders and could be available for selection*".

Therefore, we presented to the panels a scenario in which a healthy patient is planning to go through a multifactorial PGD, accumulating oocytes for some period by a reasonable number of OCR cycles, and asked them to evaluate the likelihood that, within 20 years, such a patient would be able to have more than 50, 100 and 150 embryos for PGD selection. Both panels were skeptical regarding the likelihood of having at least 50 embryos to enable wide selection, although 8 (4 Israelis and 4 Spaniards) out of 25 doctors considered it as a possible scenario (marked 6 or more). Moreover, they were utterly skeptical regarding the other two options (100 and 150 embryos).

Table 3. Regulations of PGD and genetic engineering

	Israel (n=12)		Spain (n=13)		Mann-Whitney test		
Regulations (Q8)**	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect size**
Allow PGD for neurological disorders	8.1	2.35	7.8	1.34	56.5	p=0.228	r=-0.241
Fund PGD for neurological disorders	7.5	2.47	6.5	1.81	50.5	p=0.130	r=-0.303
Allow PGD for cancerous diseases	8.2	2.37	8.4	1.33	71.5	p=0.715	r=-0.073
Fund PGD for cancerous diseases	6.9	2.31	6.8	2.12	74	p=0.825	r=-0.044
Allow PGD for cardiovascular diseases	7.5	2.24	7.4	1.71	69	p=0.817	r=-0.100
Fund PGD for cardiovascular diseases	6.6	2.43	5.5	2.07	55.5	p=0.214	r=-0.248
Allow PGD for eyes/skin/hair color	2.7	1.97	1.6	0.77	55	p=0.183	r=-0.267
Fund PGD for eyes/skin/hair color	2.0	2.22	1.2	0.38	68.5	p=0.459	r=-0.148
Allow PGD for height/body type	2.3	1.66	1.5	0.66	62	p=0.343	r=-0.190
Fund PGD for height/body type	1.5	1.17	1.2	0.38	69.5	p=0.507	r=-0.133
Allow PGD for cognitive traits	2.0	1.35	1.6	0.77	70	p=0.634	r=-0.095
Fund PGD for cognitive traits	1.8	1.47	1.3	0.48	65.5	p=0.422	r=-0.161
Allow genetic engineering	4.0	2.86	5.0	2.61	62.5	p=0.393	r=-0.171
Fund genetic engineering	3.3	2.30	2.8	2.51	66.5	p=0.517	r=-0.130

* Significant p-values are marked in bold.
** From 1-not probable to 10-extremely probable

Table 3 presents the panels' views on whether governments should allow and fund PGD procedures corresponding with the progress of genomics in the next 20 years. The intention was to learn about their willingness or disapproval in case they were "wearing the regulator's hat", since strong disapproval from providers' perspective may seriously hinder the practice of a specific procedure. We found a strong consensus between the experts regarding allowing and funding PGD for medical reasons, with a higher tendency to allow procedures than to fund them.

According to Wilcoxon signed-rank tests, the experts were significantly less supportive of using PGD for cardiovascular diseases in comparison with PGD for cancerous diseases (p=0.008, r=-0.531 regarding the "allow" dimension and p=0.023, r=-0.453 for "funding") and neurological disorders (p=0.055, r=-0.384 and p=0.006, r=-0.552 respectively), while no differences were found between cancerous and neurological diseases (p=0.223, r=-0.243 for allow and p=0.796, r=-0.052 for fund). Some experts claimed that cardiovascular diseases, as well as neurological disorders, are influenced by many genes. However, as stated by one expert, cardiovascular diseases are "*more subject to lifestyle and environment and can be quite effectively prevented or treated*". Most doctors strongly opposed using PGD for any non-medical reason, which may, therefore, be interpreted as an unrealistic scenario for the next 20 years. Nonetheless, there was no strong consensus with respect to allowing

CRISPR/CAS in this period, with many experts willing to allow and even fund it, while others remained very cautious about it.

Table 4. Advantage of a "genetically selected person" (Q9)**

	Israel (n=12)		Spain (n=13)		Mann-Whitney test		
	Mean	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect size**
In the late stages of life (Cancer, Alzheimer etc.)	7.3	1.96	7.2	2.27	76.5	p=0.934	r=-0.017
Throughout life (better overall health)	6.1	2.43	6.1	2.43	77.5	p=0.978	r=-0.005
In childhood (regarding diseases)	5.0	2.22	6.7	2.69	48.5	p=0.105	r=-0.324
Intellectual and cognitive characteristics	4.6	2.54	2.9	2.47	36.5	**p=0.036**	r=-0.427
Physical traits - Appearance and body type	3.6	2.42	2.4	2.36	38.5	**p=0.037**	r=-0.427
Average Q9	5.4	1.56	5.0	1.77	65	p=0.503	r=-0.142

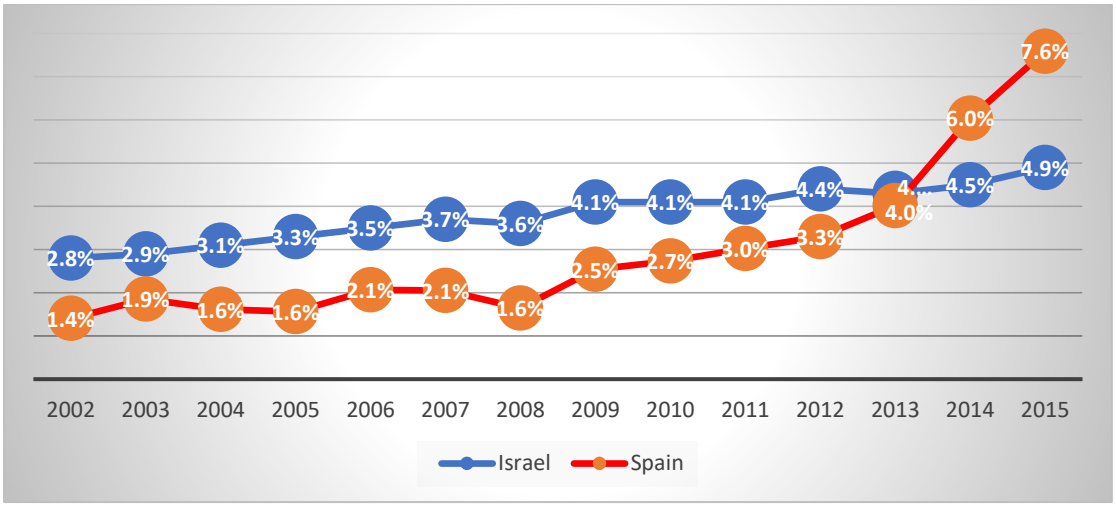
* Significant p-values are marked in bold.
* From 1-No advantage; 10-Very significant advantage

In the most speculative question (Q9), we asked the experts how the advantages of a "genetically selected person" would be expressed in 20 years regarding five categories. As shown in Table 4, the panels forecasted that PGD to prevent multifactorial diseases could produce some health advantage. This was mainly associated with late stages of life, but also, albeit to a lesser extent throughout adult life and childhood. In contrast, the experts did not attribute significant advantages to PGD for physical traits or cognitive enhancement, although the Israeli panel was more positive regarding these two aspects.

2.4.3 Demand

In the last section of the questionnaire, the experts were shown Figure 1 and asked to forecast the share of IVF births in their countries within 20 years, and the percentage of IVF births that would involve PGD (or any genetic testing/screening which aims to identify disorder or traits) (Q10). They were also asked to rank factors explaining the potential increase in demand for IVF (Q11). Results from these two questions are shown in Table 5.

Figure 1. IVF births as a share of total births



Sources: SEF (2016), Health Ministry of Israel (2018)

Table 5. Demand for IVF and PGD

	Israel (n=10)		*Spain (n=13)*		Mann-Whitney test		
Within 20 years (%) (Q10)	**Mean**	**SD**	**Mean**	***SD***	**U**	**Sig.***	**Effect size**
IVF as a share of total births	14.3%	8.12	19.0%	8.30	42	p=0.147	r=-0.302
PGD as a share of total IVF cycles	34.2%	24.74	47.3%	27.88	50.5	p=0.363	r=-0.189
Reasons for future Increase in demand (Q11)*	**Mean**	**SD**	**Mean**	**SD**	**U**	**Sig.***	**Effect size**
Decreased fertility due to aging	9.3	1.41	10.0	0.00	42	p=0.094	r=-0.365
Decreased fertility due to environmental hazards and unhealthy lifestyle	6.3	2.25	7.0	1.81	38.5	p=0.403	r=-0.187
Increased demand for PGD	7.0	2.62	6.2	1.34	37.5	p=0.397	r=-0.189
Sperm donation	5.0	1.51	4.2	1.80	32.5	p=0.204	r=-0.284
Genetic Engineering	2.5	0.93	2.7	0.98	44	p=0.698	r=-0.087

* Significant p-values are marked in bold.
** From 10-highest impact to 1-least impact

With a weak consensus between the panels, the Israelis forecasted, on average, a share of 14.3% for IVF births and 34.2% for PGD, while the Spaniards forecasted 19% and 47.3% respectively. Concerning the causes, the panels ranked, with a very strong consensus, decreased fertility due to aging (late pregnancies, including oocyte donation) as the main reason explaining the potential increase in demand for IVF. This was followed by both decreased fertility (due to environmental hazards and unhealthy lifestyle) and increased demand for PGD (with no statistical difference between the two; p=0.590, r=-0.121). Sperm donation was marked fourth, and genetic engineering last.

2.5. Discussion and conclusions

The first forecast given by the experts is a sharp increase in IVF success rates, although the Spanish panel was significantly more optimistic than the Israeli. These disparities can be attributed to the characteristics of the ART market development in both countries. Firstly, the Israeli ART industry is mostly publicly funded, although more than 50% of interventions are provided by private clinics (State Comptroller, 2012). The number of IVF cycles per population is the highest in the world partly because public funds cover treatments for women up to 44 years old. Also, for this reason, among others, patients older than 40 years do not easily opt for egg donation as a solution and prefer to repeat treatments (this age group stands for 40% of IVF cycles). This creates a burden on clinics and leads to low success rates (Kol et al., 2016).

Conversely, in Spain, most treatments are privately funded, and private clinics dominate the field. 35% of IVF cycles are conducted with patients older than 40, who tend to quickly approach donor-egg cycles following failed attempts with their own eggs. These cycles (donor-eggs) provide the highest success rates and also urge the practice of cryopreservation (SEF, 2016). Additionally, Spain had a quick expansion since 2009 (as shown in Figure 1), while in Israel the ART market grew more moderately in recent years.

In addition, the composition of the samples forming our panels may cause a lower degree of optimism regarding technological developments among the Israeli experts, as they mostly operate in average-budget clinics and with patients of advanced reproductive age who repeat cycles with their own eggs and low success rates. Meanwhile, Spanish experts in the sample are affiliated with private clinics with access to the latest technologies. They also more often approach women in advanced reproductive age with donor-eggs which provide higher success rates. However, despite expressing distinct levels of expectations, the overall direction of the forecast is similar for both panels. The experts anticipate lack of significant breakthroughs in the first stage of IVF (oocyte retrieval) but hold high expectations regarding cryopreservation of eggs, which may provide some new demand channels (see Dondorp et al., 2012; Bhatia & Campo-Engelstein, 2018). This view is also aligned with Casper et al. (2017), who highlight an improvement in quality but not in quantity of eggs, which may delay some of the radical scenarios linked with ART.

Nevertheless, concerning the other stages of IVF (fecundation and implantation), the experts in both panels anticipated that the average-budget clinics would close the gap with today's premium ones, which suggests that IVF is evolving from a "pre-paradigmatic stage" to a "paradigmatic stage", where a generally accepted scientific approach is gaining ground (Teece, 1986).

The experts' second major forecast is a continuous increase in demand, which could mark the evolution of IVF into the paradigmatic stage, although in this respect too, the Spanish panel holds higher expectations. Nevertheless, the experts' average forecast that 16.5% of births in their countries will result from IVF within 20 years is not surprising nor extreme, but rather consistent with current trends as marked by latest reports by the Spanish Society of Fertility (SEF) and the Health Ministry of Israel, and with an estimated 10-15% rate of infertility (Agarwal et al., 2015; ASRM, 2015).

Conversely, experts' estimation that 39% of IVF procedures will include PGD is strikingly high in comparison with current rates of under 5%. Such an increase could be driven by the introduction of PGD to a larger number of polygenic, late-onset diseases (Pavone & Arias, 2012; Altarescu et al., 2015; Knoepfler, 2016), and by the growing use of PGS. This is because PGS requires a biopsy and, once taken, it might be hard to prevent its use for PGD. Additionally, the improvement of PGS may occur by reducing the scale of screening, focusing on shorter sections of DNA, which, in a way represents an approximation towards diagnosis. Despite the experts' favorable anticipations for PGS, there are many concerns regarding its efficiency because embryo mosaicism (the presence of two or more populations of cells) may lead to a false-positive error, ending up wasting good embryos (Orvieto, 2016; Orvieto & Gleicher, 2016; Casper et al., 2017).

According to the latest ART report from the U.S., 22% of ART cycles in 2016 involved PGD/PGS (CDC, 2016). Hence, PGS is gaining popularity in the second largest ART industry (following Japan), a trend which could be soon followed by other countries. Thus, the expected growing use of PGD/PGS should bring the attention of regulators to the principal-agent problem, since asymmetric information in this context may potentially lead to supplier-induced demand whereby physicians in pursuit of monetary profits treat patients beyond the point where they might benefit (Cutler et al., 2017). Furthermore, despite the slow diffusion of PGD, PGS is expanding quickly opening up new challenges for regulators since the use of PGS may erode current legislation by bringing in PGD from the back door.

In this matter, it is also important to remind that IVF-conceived babies, and those subject to PGD/PGS, might be exposed to a higher risk of cancerous and cardiovascular diseases, developmental deficiencies, and cognitive disorders, requiring careful follow up of these children into adulthood to determine long-term health consequences and epigenetic modifications (ESHRE, 2014; Fauser et al., 2014; Nuffield Council on Bioethics, 2018). As explained by one of the experts in our study, the problem with the epidemiology of IVF is that humans have a relatively long lifecycle. It is therefore hard to find clear evidence to confirm or reject the long-term concerns regarding these procedures (PGD was introduced in 1990 and ICSI in 1992). Likewise, it will take time to confirm evidence of health benefits if expanded PGD is practiced with such aim, and that is why some of the developments

described in this paper will also be marked by socio-technical imaginaries, forming users' perception of health benefits backed (or not) by scientific promises (Rommetveit, 2011; Tarkkala et al., 2018).

The third key forecast emanating from our study relates to the geneticization of reproduction. Both panels quite similarly anticipated some benefits from an expanded PGD in the next 20 years, including diagnosis for multifactorial diseases. However, the limited number of oocytes available to produce embryos for selection remains a critical barrier, as also suggested by previous research (Greely, 2016; Nuffield Council on Bioethics, 2018). Alternatively, the experts were more confident regarding the use of GE by CRISPR/CAS as a better alternative to PGD, although most experts were not rushing to allow clinical use of GE, and also doubted that it would provoke any radical scenario within a 20-year timescale. CRISPR/CAS is seen as a promising technology, but it also holds some great uncertainties, as germline modification carries significant risks for unintended side effects, which will only be recognized in future generations. Once such a destructive gene edit is introduced to the germline, there is currently no method to remove it (Evitt et al., 2015; Nuffield Council on Bioethics, 2018).

Our forecasts are exposed to some methodological limitations, such as the selection of experts as a source of information (who is an expert and how biased is his/her opinion?) (Devaney & Henchion, 2018) and the use of consensus to approach the truth, which are common concerns with the Delphi method (Landeta, 2006). That said, the experts in our panels are leading gynecologists and geneticists in Israel and Spain who have practiced IVF and PGD for many years, and although these countries may not represent the global scenario, they are at the forefront of the world's ART industry.

Nevertheless, it would be interesting for future studies to contrast our results against other collectives, including other kinds of stakeholders (e.g., patient associations, hospital managers, non-practitioner scientists, etc.), as well as experts from other countries. Indeed, when counting on physicians for predicting future trajectories of technologies, one must also acknowledge that the technology course might be influenced by a broader range of related aspects, such as regulations, institutional and economic factors, consumer choices, pressures from different interest groups, etc. (Brigham et al., 2013; Martin, 2014).

Altogether, the main conclusion of this study is that the expansion course of ART occurs gradually, and it is therefore unlikely that the extreme scenarios associated with ART (i.e., eugenics and the geneticization of reproduction) will fully materialize in the next two decades. However, the increasing scale of the ART industry, which is currently growing due to infertility (and not because of reproductive genetics), makes these extreme scenarios more viable. It also raises the likelihood of health risks derived from the ongoing medicalization of reproduction (Aragona et al., 2011; Orvieto, 2013; La Marca & Sunkara, 2014) and magnifies ethical dilemmas related to asymmetric information,

exploitation, donor anonymity, and social justice, among others (Johnson & Petersen, 2008; Frith & Blyth, 2014; Ravitsky, 2017). These risks will need to be carefully addressed by regulators in the years to come.

References:

Agarwal, A., Mulgund1, A., Hamada, A., & Chyatte, M. R. (2015). A Unique View on Male Infertility Around the Globe. Reproductive Biology and Endocrinology, doi 10.1186/s12958-015-0032-1.

Altarescu, G., Beeri, R. D., Eldar-Geva, T., Steinberg, A., Levy-Lahad, E., & Renbaum, P. (2015). Preimplantation Genetic Risk Reduction: A New Dilemma in the Era of Chromosomal Microarrays and Exome Sequencing. Reproductive Biomedicine Online, 5, 706-10, doi: 10.1016/j.rbmo.2015.07.002.

Amir-Aslani, A., & Mangematin, V. (2010). The Future of Drug Discovery and Development: Shifting Emphasis Towards Personalized Medicine. Technological Forecasting & Social Change, 77, 2, 203-2017, doi: 10.1016/j.techfore.2009.09.005.

Aragona, C., Mohamed, A. M., Salomè B Espinola, M., Linari, A., Pecorini, F., Micara, G., & Sbracia, M. (2011). Clinical Complications after Transvaginal Oocyte Retrieval in 7,098 IVF Cycles. Journal of Fertility and Sterility, 1, :293-4, doi: 10.1016/j.fertnstert.2010.07.1054.

ASRM, P. C. (2015). Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility, 3, e18-25, doi: 10.1016/j.fertnstert.2014.12.103.

Batzer, F. R., & Ravitsky, V. (2009). Preimplantation Genetic Diagnosis: Ethical Considerations. In V. Ravitsky, A. Fiester, & A. L. Caplan, The Penn Center Guide to Bioethics. (pp. 339-354). New York: Springer.

Bhatia, R., & Campo-Engelstein, L. (2018). The Biomedicalization of Social Egg Freezing: A Comparative Analysis of European and American Professional Ethics Opinions and US News and Popular Media. Science, Technology, & Human Values, 43(5), 864-887, doi: 10.1177/0162243918754322.

Boon, W. P., Aardenb, E., & Broerse, J. E. (2015). Path creation by public agencies — The case of desirable futures of genomics. Technological Forecasting & Social Change, 99, 67–76, doi: 10.1016/j.techfore.2015.06.038.

Brigham, K. B., Cadier, B., & Chevreul, K. (2013). The Diversity of Regulation and Public Financing of IVF in Europe and Its Impact on Utilization. Human Reproduction, 28(3),666-75, doi: 10.1093/humrep/des418.

Buchanan, A., Brock, D. W., Daniels, N., & Wikler, D. (2000). From Chance to Choice: Genetics and Justice. Cambridge University Press.

Cai, Q. F., Wan, F., Huang, R., & Zhang, H. W. (2011). Factors Predicting the Cumulative Outcome of IVF/ICSI Treatment: A Multivariable Analysis of 2450 Patients. Human Reproduction, 9, 2532-40. doi: 10.1093/humrep/der228.

Casper, R., Haas, J., Hsieh, T., Bassil, R., & Mehta, C. (2017). Recent Advances in in Vitro Fertilization. F1000Research, 6, 1616, doi: 10.12688/f1000research.11701.1.

CDC. (2018). Assisted Reproductive Technology - National Summary Report 2016. Atlanta, US, Centers for Disease Control and Prevention, American Society for Reproductive Medicine, https://www.cdc.gov/art/pdf/2016-report/ART-2016-National-Summary-Report.pdf.

Chambers, G. M. et al., (2014). The Impact of Consumer Affordability on Access to Assisted Reproductive Technologies and Embryo Transfer Practices: An International Analysis. Fertility and Sterility, 101(1), 191-198, doi: 10.1016/j.fertnstert.2013.09.005.

Chatterji, A. K., Fabrizio, K. R., Mitchell, W., & Schulman, K. A. (2008). Physician-Industry Cooperation in The Medical Device Industry. Health Affairs, 6, 1532-43, doi: 10.1377/hlthaff.27.6.1532.

Christensen, K. D., Dukhovny, D., Siebert, U., & Green, R. C. (2015). Assessing the Costs and Cost-Effectiveness of Genomic Sequencing. The Journal of Personalized Medicine, 5, 470-486; doi 10.3390/jpm5040470.

Cobo, A., Garcia-Velasco, J., Domingo, J., Remohí, J., & Pellicer, A. (2013). Is Vitrification of Oocytes Useful for Fertility Preservation for Age-Related Fertility Decline and in Cancer Patients? Fertility and Sterility, 99(6),1485-95, doi: 10.1016/j.fertnstert.2013.02.050.

Cutler, D., Skinner, L., Stern, D., & Wennberg, D. (2017). Physician Beliefs and Patient Preferences: A New Look at Regional Variation in Health Care Spending. AEJ: Economic Policy (forthcoming); NBER, Working Paper No. 19320, doi: 10.3386/w19320.

Dayé, C. (2018). How to Train Your Oracle: The Delphi Method and its Turbulent Youth in Operations Research and the Policy Sciences. Social Studies of Science, 48(6), 846–868, doi: 10.1177/0306312718798497.

Devaney, L., & Henchion, M. (2018). Who is a Delphi 'Expert'? Reflections on a Bioeconomy Expert Selection Procedure from Ireland. Futures, 99, 45–55, doi: org/10.1016/j.futures.2018.03.017.

Di Stefano, G., Gambardella, A., & Veronab, G. (2012). Technology Push and Demand-Pull Perspectives in Innovation Studies: Current Findings and Future Research Directions. Research Policy, 41(8), 1283-1295, doi: 10.1016/j.respol.2012.03.021.

Dondorp, W., de Wert, G., Pennings, G., Shenfield, F., Devroey, P., Tarlatzis, B., . . . Diedrich, K. (2012). Oocyte Cryopreservation for Age-Related Fertility Loss. Human Reproduction, 5, 1231-7, doi: 10.1093/humrep/des029.

Dosi, G. (1982). Technological Paradigms and Technological Trajectories: A Suggested Interpretation of the Determinants and Directions of Technical Change. Research Policy, 11(3): 147-162, doi: 10.1016/0048-7333(82)90016-6.

ESHRE. (2012). Assisted Reproductive Technology in Europe, 2007: Results Generated from European Registers by ESHRE. Human Reproduction, 4, 954-66. doi: 10.1093/humrep/des023.

ESHRE. (2018). Assisted Reproductive Technology in Europe, 2014: Results Generated from European Registers by ESHRE. Human Reproduction, 33, 9, 1586–1601, doi: 10.1093/humrep/dey242.

ESHRE Capri Workshop Group. (2014). Birth Defects and Congenital Health Risks in Children Conceived Through Assisted Reproduction Technology (ART): A Meeting Report. Journal of Assisted Reproduction and Genetics, 8, 947-58, doi: 10.1007/s10815-014-0255-7.

Evitt, N. H., Mascharak, S., & Altman, R. B. (2015). Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework. The American Journal of Bioethics, 15(12): 25–29, doi: 10.1080/15265161.2015.1104160.

Fauser, B. C., Nargund, G., Andersen, A. N., Norman, R., Tarlatzis, B., Boivin, J., & Ledge, W. (2010). Mild Ovarian Stimulation for IVF: 10 Years Later. Human Reproduction, 11, 2678-84. doi: 10.1093/humrep/deq247.

Fauser, B. C., P., D., Diedrich, K., B. B., Bonduelle, M., Delemarre-van de Waal, H. A., . . . Wells, D. (2014). Health Outcomes of Children Born After IVF/ICSI: A Review of Current Expert Opinion and Literature. Reproductive BioMedicine Online, 2, 162-82, doi: 10.1016/j.rbmo.2013.10.013.

Field, A. (2009). Discovering Statistics Using SPSS. Los Angeles: Sage.

Fritz, C. O., & Morris, P. E. (2012). Effect Size Estimates: Current Use, Calculations, and Interpretation. Journal of Experimental Psychology: General, 141, 1, 2–18, doi: 10.1037/a0024338.

Fukuyama, F. (2002). Our Posthuman Future, Consequences of the Biotechnology Revolution. New York: Farrar, Straus and Giroux.

Garland-Thomson, R. (2015). Human Biodiversity Conservation: A Consensual Ethical Principle. The American Journal of Bioethics, 15(6):13-5. doi: 10.1080/15265161.2015.1028663.

Godinho, M. M. (2016). Uma Brevíssima História do Futuro - Ensaio Sobre Como Limitar os Futuros Possíveis a Futuros Preferíveis. ISEG - Lisbon School of Economics and Management.

Greely, H. T. (2016). The End of Sex and the Future of Human Reproduction. Cambridge: Harvard University Press.

Habermas, J. (2003). The Future of Human Nature. Cambridge: The translation polity press.

Harari, Y. N. (2016). Homo Deus: A brief history of tomorrow. London: Harvill Secker.

Harmon, S. H. (2016). Modernizing Biomedical Regulation: Foresight and Values in the Promotion of Responsible Research and Innovation. Journal of Law and the Biosciences, 680–686, doi: 10.1093/jlb/lsw053.

Harris, J. (2011). Taking the 'Human' out of Human Rights. Cambridge Quarterly of Healthcare Ethics, 20 (1) 9-20 doi: 10.1017/S0963180109990570.

Health Ministry of Israel. (2018). In Vitro Fertilization (IVF) Treatments 1990-2016. Israel: Facilities and Equipment Licensing Division, Health Information Division, https://www.health.gov.il/PublicationsFiles/IVF1990_2016.pdf.

Hubbard, R. (1993). Predictive Genetics and the Construction of The Healthy Ill. Suffolk U. L. Rev, 27(4):1209-24.

Inhorn, M. C., Birenbaum-Carmeli, D., & Patrizio, P. (2017). Medical Egg Freezing and Cancer Patients' Hopes: Fertility Preservation at the Intersection of Life and Death. Social Science & Medicine, 195; 25-33; doi: org/10.1016/j.socscimed.2017.10.031.

Ishihara, O. e. (2019). Assisted reproductive technology in Japan: A summary report for 2016 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol., 1, 7–16, doi: 10.1002/rmb2.12258.

Johnson, L. (2014). Regulation of Assisted Reproductive Treatment (ART) in Australia & Current Ethical Issues. Indian Journal of Medicine Research, 140, 9-12.

Johnson, M., & Petersen, K. (2008). Public Interest or Public Meddling? Towards a Subjective Framework for the Regulation of Assisted Reproduction Technologies. Human Reproduction, 3, 716-28, doi: 10.1093/humrep/dem387.

Jonas, H. (1984). The Imperative of Responsibility. University of Chicago.

Klitzman, R. (2008). Anticipating Issues Related to Increasing Preimplantation Genetic Diagnosis Use: A Research Agenda. Reproductive BioMedicine Online, 17, 1, 33-42, doi: 10.1016/S1472-6483(10)60188-5.

Knoepfler, P. (2016). GMO Sapiens, The Life-Changing Science of Designer Babies. Singapore: World Scientific Publishing.

Koch, T. (2001). Disability and Difference: Balancing Social and Physical Constructions. Journal of Medical Ethics, 27(6): 370–376, doi: 10.1136/jme.27.6.370.

Kol, S., Bergovoy, L., Yellin, Segal, Y., & Porath, A. (2016). In Vitro fertilization (IVF) treatments in Maccabi Healthcare Services 2007-2014. Israel Journal of Health Policy Research, 5:14, doi: 10.1186/s13584-016-0072-9.

Kovac, J., R. Addai, J., Smith, R. P., Coward, R. M., Lamb, D. J., & Lipshultz, L. I. (2013). The Effects of Advanced Paternal Age on Fertility. Asian Journal of Andrology, 15, 723–728, doi: 10.1038/aja.2013.92.

Krimsky, S. (2019). Ten Ways in Which He Jiankui Violated Ethics. Nature Biotechnology, 37, 19, doi: org/10.1038/nbt.4337.

La Marca, A., & Sunkara, S. K. (2014). Individualization of Controlled Ovarian Stimulation in IVF Using Ovarian Reserve Markers: From Theory to Practice. Human Reproduction Update, 20(1), 124-40, doi: 10.1093/humupd/dmt037.

Landeta, J. (2002). El Método Delphi, Una téecnica de previsión del futuro. Barcelona: Ariel.

Landeta, J. (2006). Current Validity of the Delphi Method in Social Sciences. Technological Forecasting & Social Change, 73(5), 467–482 doi: 10.1016/j.techfore.2005.09.002.

Landeta, J., J., M., Ruíz, V., & Galter, J. (2008). Results of a Delphi Survey in Drawing Up the Input–Output Tables for Catalonia. Technological Forecasting & Social Change, 75(1), 32–56, doi: org/10.1016/j.techfore.2007.01.005.

Landeta, L., Barrutia, J., & Lertxundi, A. (2011). Hybrid Delphi: A Methodology to Facilitate Contribution from Experts in Professional Contexts. Technological Forecasting & Social Change, 78(9) 1629–1641, doi: org/10.1016/j.techfore.2011.03.009.

Ledford, H. (2017). CRISPR Fixes Disease Gene in Viable Human Embryos, Gene-Editing Experiment Pushes Scientific and Ethical Boundaries. 548, 13–14, doi: 10.1038/nature.2017.22382: Nature.

Lemoine, M.-E., & Ravitsky, V. (2015). Sleepwalking into Infertility: The Need for a Public Health Approach Toward Advanced Maternal Age. The American Journal of Bioethics, 15(11):37-48. doi: 10.1080/15265161.2015.1088973.

Lewis, C. S. (1947). The Abolition of Man. New York: Oxford University Press.

Lippman, A. (1991). Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities. American Journal of Law and Medicine, 17(1-2):15-50.

Lu, L., Lv, B., Huang, K., Xue, Z., Zhu, X., & Fan, G. (2016). Recent Advances in Preimplantation Genetic Diagnosis and Screening. Journal of Assisted Reproduction and Genetics, 33, 9,1129–1134, doi: 10.1007/s10815-016-0750-0.

Machado, M. P., & Galdeano, A. S. (2011). Coverage of Infertility Treatment and Fertility Outcomes: Do Women Catch Up? Bonn, Germany: IZA Discussion, Paperhttp://ftp.iza.org/dp5783.pdf.

Majumdar, A., & Tiwari, N. (2014). Environment and Infertility. In A. R. Kamini, H. Carp, R. Fischer, & K. Deepika, Principles and Practice of Assisted Reproductive Technology (pp. 320-329). New Delhi: Jaypee Brothers Medical Publishers.

Marchant, G. E. (2011). The Growing Gap Between Emerging Technologies and the Law. In G. E. Marchant, B. R. Allenby, & J. R. Herkert, The Growing Gap Between Emerging Technologies and Legal-Ethical Oversight (pp. 19-33). Dordrecht: Springer.

Martin, L. J. (2014). The World's Not Ready for This: Globalizing Selective Technologies. Science, Technology, & Human Values, 39(3) 432-455, doi: 10.1177/0162243913516014.

Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS Medicine, 9(12), e1001356, doi: 10.1371/journal.pmed.1001356.

Mathews, T. J., & Hamilton, B. E. (2016). Mean Age of Mothers is on the Rise: United States, 2000-2014. Centers for Disease Control and Prevention, National Center for Health Statistics: NCHS Data Brief, No. 232.

Mayor, B., Casada, R. R., L. J., López-Gunn, E., & Villarroya, F. (2016). An Expert Outlook on Water Security and Water for Energy Trends to 2030–2050. Water Policy, 18(1) 1-18; doi: 10.2166/wp.2015.196.

Melander, L. (2018). Scenario Development in Transport Studies: Methodological Considerations and Reflections on Delphi Studies. Futures, 96, 68–78, doi: org/10.1016/j.futures.2017.11.007.

Mewes, F. (2002). Regulations for the Human Park: On Peter Sloterdijk's Regeln für den Menschenpark. Concordia University, Gnosis, 6(1).

Milachich, T. (2014). New Advances of Preimplantation and Prenatal Genetic Screening and Noninvasive Testing as a Potential Predictor of Health Status of Babies. BioMed Research International, 306505. doi: 10.1155/2014/306505.

Nuffield Council on Bioethics. (2018). Genome Editing and Human Reproduction: Social and Ethical Issues. London.

OECD. (2018). https://stats.oecd.org/.

Okoli, C., & Pawlowski, S. D. (2004). The Delphi Method as a Research Tool: An Example, Design Considerations and Applications. Information & Management, 42(1), 15–29, doi: 10.1016/j.im.2003.11.002.

Orvieto, R. (2013). Ovarian Hyperstimulation Syndrome- An Optimal Solution for an Unresolved Enigma. Journal of Ovarian Research, 5; 6(1), 77. doi: 10.1186/1757-2215-6-77.

Orvieto, R. (2016). Preimplantation Genetic Screening- The Required RCT That Has Not Yet Been Carried Out. Reproductive Biology and Endocrinology, 14:35, doi 10.1186/s12958-016-0171-z.

Orvieto, R., & Gleicher, N. (2016). Should Preimplantation Genetic Screening (PGS) be Implemented to Routine IVF Practice? Journal of Assisted Reproduction and Genetics, 11, 1445-1448, doi: 10.1007/s10815-016-0801-6.

Palermo, G. D., Neri, Q. V., Takeuchi, T., & Rosenwaks, Z. (2009). ICSI: Where We Have Been and Where We Are Going. Seminars in Reproductive Medicine, 2, 191-201, doi: 10.1055/s-0029-1202309.

Palm, E., & Hansson, S. O. (2006). The Case for Ethical Technology Assessment (eTA). Technological Forecasting & Social Change, 73, 543–558, doi: 10.1016/j.techfore.2005.06.002.

Pavone, V., & Arias, F. (2012). Beyond the Geneticization Thesis: The Political Economy of PGD/PGS in Spain. Science, Technology, & Human Values, 37(3) 235-261, doi: 10.1177/0162243911411195.

Peters, M., Schneider, M., Griesshaber, T., & Hoffmann, V. H. (2012). The Impact of Technology-Push and Demand-Pull Policies on Technical Change – Does the Locus of Policies Matter? Research Policy, 41(8), 1296-1380, doi: org/10.1016/j.respol.2012.02.004.

Practice Committee of the Society for Assisted Reproductive Technology (SART) & Practice Committee of the American Society for Reproductive Medicine (ASRM). (2008). Preimplantation Genetic Testing: A Practice Committee Opinion. Fertility and Sterility, 90, (5 Suppl), S136-43, doi: 10.1016/j.fertnstert.2008.08.062.

Ramsey, P. (1972). Shell we "Reproduce"? JAMA, 220 (10), 1346-1350; (11), 1481-1485.

Ravitsky, V. (2012). Conceived and Deceived: The Medical Interests of Donor-Conceived Individuals. Hasting Center Report, 42(1), 17-22, doi: 10.1002/HAST.9.

Regalado, A. (2017, November 1). Eugenics 2.0: We're at the Dawn of Choosing Embryos by Health, Height, and More. MIT Technology Review, https://www.technologyreview.com/s/609204/eugenics-20-were-at-the-dawn-of-choosing-embryos-by-health-height-and-more/?utm_source=pocket&utm_medium=email&utm_campaign=pockethits.

Ribeiro, B. E., & Quintanilla, M. A. (2015). Transitions in Biofuel Technologies: An Appraisal of the Social Impacts of Cellulosic Ethanol Using the Delphi Method. Technological Forecasting & Social Change, 92, 53–68, doi: 10.1016/j.techfore.2014.11.006.

Rip, A., & Schot, J. W. (2002). Identifying Loci for Influencing the Dynamics of Technological Development. In R. W. K.H. Sorensen, shaping technology, guiding policy. Concepts, spaces and tools. Cheltenham: Edward Elgar.

Rogers, E. M. (1983). Diffusion of Innovation, Third Edition. New York: The Free Press.

Rommetveit, K. (2011). Genetic Enhancement, Futures Tense. Futures, 43, 76–85, doi: 10.1016/j.futures.2010.10.014.

Savulescu, J. (2001). Procreative Beneficence: Why We Should Select the Best Children? Bioethics, 15(5-6), 413-26, doi: 10.1111/1467-8519.00251.

SEF. (2016). Registro Nacional de Actividad - Técnicas de Reproducción Asistida, Informe estadístico de Técnicas de Reproducción Asistida 2016. https://www.registrosef.com/public/docs/sef2016_IAFIVm.pdf: Sociedad Española de Fertilidad.

Shulman, C., & Bostrom, N. (2014). Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer? Global Policy, 5(1) 85-92, doi: 10.1111/1758-5899.12123.

Skirton et al. (2013). A Delphi Study to Determine the European Core Curriculum for Master Programmes in Genetic Counselling. European Journal of Human Genetics, 21, 1060–1066, Doi: 10.1038/ejhg.2012.302.

State Comptroller. (2012). In-Vitro Fertilization - Annual Report (63λ).

Swanson, A., Lau, E., & Strawn, E. (2007). Preimplantation Genetic Diagnosis: Technology and Clinical Applications. Wisconsin Medical Journal, 106(3):145-51.

Tarkkala, H., Helén, I., & Snell, K. (2018). From Health to Wealth: The Future of Personalized Medicine in the Making. Futures, doi: org/10.1016/j.futures.2018.06.004.

Teece, D. J. (1986). Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy. Research Policy, 15(6), 285-305, doi: 10.1016/0048-7333(86)90027-2.

Toiviainen, H., Jallinoja, P., Aro, A. R., & Hemminki, E. (2003). Medical and lay Attitudes Towards Genetic Screening and Testing in Finland. European Journal of Human Genetics, 11, 565–572, doi: 10.1038/sj.ejhg.5201006.

Von der Gracht, H. A. (2012). Consensus Measurement in Delphi Studies Review and Implications for Future Quality Assurance. Technological Forecasting & Social Change, 79(8), 1525–1536, doi: 10.1016/j.techfore.2012.04.013.

Von Hippel, E. (2005). Democratizing Innovation. London: The MIT Press.

Wailoo, K., & Pemberton, S. (2006). The Troubled Dream of Genetic Medicine. Baltimore: The Johns Hopkins University Press.

Walsh, V. (1983). Invention and Innovation in the Chemical Industry: Demand-Pull or Discovery-Push? Research Policy, 13(4) 211-234, doi: 10.1016/0048-7333(84)90015-5.

Wang, Z. (2014). Automatic Zona Pellucida Dissection Position Selection for Embryo Biopsy in Pre-implantation Genetic Diagnosis. International Conference on Robotics and Biomimetics (pp. 475-480). Bali: IEEE.

Wilkinson, S. (2015). Prenatal Screening, Reproductive Choice, and Public Health. Bioethics, 1, 26-35. doi: 10.1111/bioe.12121.

Zlotogora, J. (2014). Genetics and Genomic Medicine in Israel. Molecular Genetics & Genomic Medicine, 2(2): 85–94, doi: 10.1002/mgg3.73.

Zuckerman, S., Zeevi1, D. A., Gooldin, S., & Altarescu, G. (2017). Acceptable Applications of Preimplantation Genetic Diagnosis (PGD) among Israeli PGD Users. European Journal of Human Genetics, 25, 1113–1117, doi: 10.1038/ejhg.2017.113.

3. REGULATORY RESPONSES TO ASSISTED REPRODUCTIVE TECHNOLOGY: A COMPARATIVE ANALYSIS OF SPAIN AND ISRAEL

3.1. Introduction

Assisted Reproductive Technologies (ART) such as In-Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) already account for more than 4% of yearly national births in some countries including Spain and Israel (ESHRE, 2018; Health Ministry of Israel, 2018). With further improvements and higher success rates, this share is projected to keep growing, considering that infertility rates amount to 8-15% of the general population (Spar, 2006; ASRM, 2015; Agarwal et al., 2015), and are fueled by environmental factors and the rising age of parenthood (Boivin et al, 2007; Mascarenhas et al., 2012; Johnson, 2014; Inhorn & Patrizio, 2015; Sobotka, 2016).

Technological trajectories in ART have been shaping and stimulating the market, creating new expectations, and often generating more complex ethical dilemmas. For example, abilities to control fertility by cryopreservation or to determine its outcome by genetic selection are broadening the motivations to approach IVF beyond the desire to solve infertility. Developments in genomics, genetic engineering, and stem-cells could further boost the ART industry and add to the complexity of its regulation (Shulman & Bostrom, 2014; Knoepfler, 2016). The regulatory approach adopted by governments needs to cope with a constantly changing technical frontier and a certain level of uncertainty concerning the risks and benefits of ART, as is also the case with other emerging technologies (Garden and Winickoff, 2018).

The aim of this paper is twofold: to identify those factors affecting regulations and priority setting, and to review the regulatory responses to technological and market developments in Israel and Spain. These countries offer a fertile ground for comparative analysis since they are amongst the most active users of ART (ESHRE, 2018; SEF, 2016; Health Ministry of Israel, 2018). Moreover, in both countries, policymakers have expressed fewer serious ethical and moral restrictions towards this field in comparison with other western countries (Teman, 2010; Brigham et al., 2013), but have also developed different regulatory frameworks reflecting their different cultures and institutional contexts. This study can be framed within the concern voiced recently in the academic literature highlighting the importance of “regulatory assessment” of medical technologies (Ho et al., 2016; Hofer et al., 2015). It also builds upon the existing literature that has engaged in comparative analyses of ART regulations in the U.S., Canada, the U.K. and other European countries (Nelson, 2006; Brigham et al., 2013; Pennings et al., 2014; Präg & Mills, 2017; Jasanoff & Metzler, 2018).

We began by developing a conceptual framework to identify the main regulatory dimensions and categorizing the potential factors affecting regulatory behaviors. Then, we conducted a comparative review of ART regulations. Our research included a Delphi survey combined with in-depth interviews. The Delphi method is a prospective technique widely used for getting information about the future and helping in decision making regarding complex problems, which is based on the answers of a panel of experts to a questionnaire. The survey is conducted in several rounds to produce iteration following controlled feedback, i.e., in each round the experts may change their replies and add comments after consulting the general views of other respondents (Von der Gracht, 2012; Mayor et al., 2016). This process allows experts to reach consensus or to suggest various alternative solutions which may be used for challenging future uncertainties (Okoli & Pawlowski, 2004; Melander, 2018). The Delphi method is then built on the knowledge, experience, and judgment tacitly residing in individual experts, and it is considered a suitable tool to replace traditional statistical models and adequate sets of data when those are not available (Landeta et al., 2008; Salazar-Elena et al., 2016).

We selected two panels of experts, where each panel represents one of the countries analyzed. These two panels were formed to simulate potential advisory committees, comprised of a range of experts from various fields related to ART, like those who traditionally accompany the legislation process. This research strategy allowed us to better understand (i) the factors affecting the different regulatory approaches used by Spain and Israel, (ii) the perceptions of experts regarding the outcomes of the regulations in place and (iii) their opinions regarding alternative measures used to prevent and cure infertility.

3.2. Analytical framework

Based on a literature review, this section classifies the critical dimensions that characterize national regulations of ART, as well as the factors that explain different regulatory choices. This analytical framework will then be used in the next sections as the prism for a comparative analysis of the cases of Israel and Spain.

3.2.1. Regulatory dimensions

We begin by presenting in Table 1 the main components of ART regulations, which can be classified considering the broader institutional settings in place, the specific regulatory controls that are introduced, and the provision of direct public support.

Table 1. Regulatory dimensions

1. Institutional settings		**References**
Regulatory agency	– Established by a parliament or a ministry, potentially with the advice of nominated committees (e.g. Spain, Israel). – Elaborated by a central statutory agency with members nominated by government in collaboration with medical and scientific societies (e.g. U.K., Australia). – A hybrid model, in which some broad laws are established by the state and a more detailed regulation is elaborated by an independent agency (e.g. U.S.).	Nelson, 2006; Clements, 2009
Regulatory approaches	– Legislation (most European countries) / Voluntary guidelines (Japan, India and the U.S.). – Pure-market approach (individual choice) / Value-influenced approach (cultural factors) / Value-based approach (society's values and ethical interest).	Johnson & Petersen, 2008; Präg & Mills, 2017
2. Regulatory controls		
Eligibility criteria and treatment standards	– Age limits. – Restrictions according to marital status and sexual orientations. – Number of embryos to be implanted. – Controlled ovarian hyperstimulation. – Number of cycles allowed.	Frith & Blyth, 2014; Johnson, 2014; Präg & Mills, 2017
Gamete donation	– Protect health of egg donors by limiting number of donations per donor and frequency. – Reduce gamete-donor commodification through limits on monetary compensation. – Avoid consanguineous marriage by limiting number of donations or their use. – Define status of donor's anonymity versus one's right to know his/her parent's identity.	Spar, 2006; Frith & Blyth, 2014; Ravitsky, 2017
Preimplantation Genetic Diagnosis or Screening (PGD/PGS)	– Genetic conditions which may be diagnosed by PGD (i.e., monogenetic or multifactorial, of early or late onset, with complete or reduced penetrance, and curable or non-curable). – Restrictions for non-medical reasons (e.g. sex selection). – Conditions under which PGS may be used.	Klitzman, 2009; Batzer & Ravitsky, 2009; Pavone & Arias, 2012
Gestational surrogacy	– Often banned or subject to strict approvals and limitations on monetary compensations. – Risk of uncontrolled development of international markets.	Birenbaum-Carmeli, 2016; Shalev et al., 2016
Fertility preservation	– Primarily used for medical reasons. – Regulated to protect women from commercial exploitation and controlling growing rush to freeze eggs for fertility postponement. – Restrictions regarding age limits (minimum and maximum) and number of cycles or eggs an individual may preserve.	Dondorp et al., 2012; Gruben, 2017; Bhatia & Campo-Engelstein, 2018

3. Direct public support		
Prevention of infertility	– Many infertility pathologies are due to diseases, environmental factors, harmful habits and aging. Public policy may include: • Epidemiological research. • Diagnosis in different stages. • Increasing public awareness regarding causes. • Financially supporting parenting at a younger age.	Boivin et al., 2007; Mascarenhas et al. 2012; Inhorn & Patrizio, 2015; Lemoine & Ravitsky, 2015
Public funding	– Depending on type of treatment (with/without donor gametes, surrogacy, fertility preservation, treatment additives). – Depending on the number of cycles. – Depending on patient's characteristics (age, marital status, sexual orientation, number of children). – Scope of supply. – Waiting lists.	Clements, 2009; Brigham et al., 2013
Activity and donor registries	– A vital source of information to enable analysis, and comparisons between countries. – Allow for the regulation of the quantity and quality of donations, the avoidance of consanguineous marriages, and the protection of donors. – Data contribution required by law or done voluntarily by clinics. – Registries collected by an official institution or formed as a private initiative. – Scope and scale of the data to be collected may be defined by law or by the collecting institution.	Frith & Blyth, 2014; Bosser et al., 2009

3.2.2. Factors influencing regulation

The four main potential public interests in regulation proposed by Johnson and Petersen (2008) will assist us to introduce the factors that shape ART regulations (Table 2). These "interests" may coexist or be at odds with one another and in turn influence different regulatory dimensions of ART. Firstly, health interest is associated with safety, well-being and protection of individual's health. Secondly, economic interest is associated with a market (rather than medical) approach. Thirdly, with regard to ethical interest it can be distinguished between state intervention on behalf of an individual and on behalf of society, such that "the greater the perceived benefit of an ART procedure to an individual, the stronger must be the public interest justification (the greater the anticipated social harm) for constraining it" (Johnson and Petersen, 2008, p. 717). Finally, socio-political interest refers to societal values commonly reflect increasing tolerance and permissiveness towards ART (Pennings, 2009; Johnson, 2014). Nevertheless, regulators should recognize values and beliefs and participate in

the process of social change (Harmon, 2016), to reduce fear, anger and adverse public debate (Habermas, 2003; Johnson & Petersen, 2008).

Table 2. Public interests influencing regulation

1. Health interest		**References**
Safety and well-being	– Of patients, egg-donors, surrogates and children. – Laws and guidelines may base on scientific evidence concerning success rates and global trends. –	Brigham et al., 2013
Prevention of infertility	– Early diagnosis. – Epidemiological studies investigating the causes of infertility. – Reduction of pollutants that affect fertility. – Preventive education via media campaigns, educational and health systems. – Social policies assisting parenting at a younger age.	Mascarenhas et al., 2012; Lemoine & Ravitsky, 2013 & 2015
Reduction of disabilities and severe genetic conditions	– Using PGD to avoid the birth of children with severe genetic conditions.	Johnson and Petersen, 2008; Davis et al., 2010
Avoiding negative impact on society's gene pool	– Given the suspicion that IVF-conceived babies (particularly ICSI) might be exposed to a higher risk of congenital damage, i.e., cancerous and cardiovascular diseases, developmental deficiencies and cognitive disorders.	ESHRE, 2014; Fauser et al., 2014
Consanguineous marriage and reproductive risk	– Limiting to the number of donations from each donor. – Elaborating donor registries.	Spar, 2006; Johnson & Petersen, 2008
Access to donor's genetic information and medical history	– Allowing children born from gamete donation access to such information may be crucial for their future well-being, considering the growing importance of precision medicine.	Ravitsky, 2017
2. Economic interest		
Availability of public resources and procedures to set priorities	– Defining the ART provision and funding by public health care.	Chambers et al., 2014
Reduction of future public health expenditure	– Preventing infertility. – Controlling adverse consequences of ART treatments, both related to children and to patients.	Davis et al., 2010; Aragona et al., 2011;

	– Using PGD to avoid the birth of children with severe genetic conditions.	Orvieto, 2013; ESHRE, 2014
Gains of efficiency	– Addressing market failures, such as asymmetric information regarding outcomes, risks and costs. – Protecting the public from cartels and monopolies.	Johnson and Petersen, 2008
Promotion of commercial activity carried out by ART clinics, research centers, pharmaceutical enterprises, investors, doctors and other agents.	– The sector's productivity and profitability may define the scope and quality of services, while its profits may also significantly contribute to the country's economic strength. – Some agents might exercise their power to influence the regulator and bend the rules in favor of larger economic profits.	Pavone & Arias, 2012; Johnson & Petersen, 2008; Präg & Mills, 2017
3. Ethical interest		
Protecting children's right to an open future	– Avoiding inappropriate uses of genetic selection or engineering to deny parents from trapping children in a life in which they have limited opportunities.	Habermas, 2003; Batzer & Ravitsky, 2009
Access to parents' identity	– Revealing a donor's identity may be important for children's autonomy and psychology.	Ravitsky, 2017
Supporting the autonomy of parents and donors	– Protecting the autonomy of parents to use technology for their benefit. – Protecting the autonomy of donors to decide regarding their anonymity.	Bergmann, 2011; Pennings et al., 2014
Supporting autonomy by securing adequate information and legal framework	– Protecting patients, donors or surrogates from exploitation by the industry. – Protecting caregivers from lawsuits under unregulated practice.	Johnson & Petersen, 2008; Harmon, 2016
4. Socio-political interest		
Religion	– Perceptions regarding embryo status. – Attitudes towards the use of gamete donation, the access of single-mothers and same-sex couples to ART. – Attitudes towards the scale and scope of genetic selection by PGD.	Pennings, 2009; Rimon-Zarfaty et al., 2011; Wert et al., 2014; Bravo-Moreno, 2017
Historical events, cultural traditions and social conventions	– Attitudes towards fertility and infertility. – Attitudes towards the reduction of disabilities by genetic selection, which may also be reflected by attitudes towards disabilities in general.	Hashiloni-Dolev & Weiner, 2008 Garland-Thomson, 2015

Perception of the public health system and social responsibility)	– Different concepts of justice and equity. – Diverse attitudes towards markets and regulation in general lead to distinct ART regulations.	Johnson & Petersen, 2008
Fertility rates	– The importance a society attributes to fertility rates. – The perception of the role of reproduction in society. – The weight individuals attribute to having genetically-related offspring.	Birenbaum-Carmeli, 2010

3.3. Empirical context

3.3.1. Background

Spain and Israel are among the most advanced and active ART industries in the world, having very pro-IVF legislation compared to most other European countries (Brigham et al., 2013; Kol et al., 2016). Both countries can be characterized as "early adopters" (Rogers, 1983) of ART services, although for different reasons. Funding policies, market structures, and some restrictions mainly differ, and each country faces different debates arising from the increased use of ART. The two have the right balance of contrast and comparability to serve as a basis for a comparative analysis using the Delphi method, which may also provide a glimpse into some trends that may be shared by ART industries around the world.

Spain is a secular state with a strong Catholic tradition. It has a national health service covering all citizens with wide-ranging benefits and high-quality services mostly free of charge, where regional authorities are entirely responsible for health care management (Bernal-Delgado et al., 2018). Since 2008, Spain has suffered a severe economic crisis with rising rates of unemployment, particularly among the younger population. Spaniards are among the oldest parents in the world, with average maternal age at childbirth up by 1.2 since 2008 reaching 32 years in 2017 (INE, 2018). Moreover, Spanish fertility rates decreased from an average of 1.5 children per woman in 2008 to 1.3 in 2017, which is the second lowest in the OECD (average 1.7). Fertility rates have decreased among women younger than 35 and doubled among women older than 40. The prevalence of single-parent families is particularly high in Spain compared with other European countries (Bravo-Moreno, 2017). The Spanish ART industry has greatly capitalized on these trends to become the largest European IVF provider. Between 2008 and 2016, the total number of IVF cycles per year increased from 38,245 to 138,553 (SEF, 2010, 2016). It also makes Spain among the highest in Europe in relative terms (ESHRE, 2018). Finally, IVF births as a share of total births climbed to 8% in 2016, among the highest in the world (ESHRE, 2018).

Israel has an approach to health services similar to that of Spain. Defined as a Jewish state, Israel has a very heterogeneous society, in which religious affiliation ranges from secularism to traditionalism and orthodoxy. It is an ethnically diverse state in which 75% of its citizens are Jewish, 17% Muslim and the rest are Christian, Druze and other. Israel has come through the crisis of 2008 more easily than Spain, and despite rising costs of living, fertility rates were not influenced, although average maternal age increased from 29.6 in 2008 to 30.4 in 2016. A combination of historical, religious and other cultural factors, in addition to ongoing military conflict, form a very pro-fertility society where reproduction plays a central role in family structure and individual's life (Teman, 2010). In 2016, an Israeli woman had on average 3.1 children, which is a much higher fertility rate than any other OECD country, this statistic reflecting a very stable trend of the last three decades. Strong economic and technological development, full public funding of ART as well as a tendency to want large families yet begin childbearing years at an advanced age (which often necessitates the use of ART) help to explain the expansion of the ART industry in Israel (Birenbaum-Carmeli, 2016). In 2016, 41,143 IVF cycles were performed, constituting 20.6 cycles per 1000 women, the highest in the world in relative terms. In 2016, the IVF share in total births was 4.7%, which is among the highest percentage in the world (Health Ministry of Israel, 2018).

3.3.2. Current regulations

Based on a review of regulatory documents and protocols/guidelines[2] and complemented by personal interviews with key agents who participated in the Delphi survey, we conducted a regulatory comparison of the two countries (Table 3) through the lens of the analytical framework developed in Section 2.1.

[2] In Spain, Law 35/1988 on Assisted Reproduction Techniques, revised by laws 10/1995 of the Penal Code and Law 45/2003. Reformed by Law 14/2006 on Assisted Reproduction Techniques and partially revised by Law 19/2015 of administrative reform measures in the field of the Administration of Justice and the Civil Registry. In Israel, Public Health Regulations (In Vitro Fertilization), 1987, revised by National Health Insurance Law, 1994; revised again by Health Ministry guidelines, 2014.

Table 3. ART regulatory comparison Israel vs. Spain

Category	Israel	Spain
Institutional settings		
Regulatory agency	Health Ministries develop regulation in both countries	
	• In some matters of funding IVF and approving the use of PGD, Health Maintenance Organizations (HMO) and Hospitals are autonomous • Public committees are appointed occasionally to examine legislation and provide advice.	• The National Committee of Human Assisted Reproduction (CNRHA) guides the use of ART and is responsible for authorizing the use of PGD. • The National Bioethics Committee is an independent consultative body, established by law and designated to issue reports, proposals, and recommendations for public authorities at the national and regional level in bioethics (including ART issues). Additionally, there are Committees at a regional level.
Legislation vs. guidelines	Both countries regulate ART mainly by legislation, leaving few issues to guidelines.	
Regulatory controls		
IVF Eligibility criteria	• Women 18-44, up to 54 (donor- egg) • Lesbian couples need to apply for recognition of parental status.	• No age limit by law, each center has its protocols, it is tacitly agreed to limit IVF treatment up to the age of 50, subject to comprehensive tests regarding risks which may arise from advanced age. • Lesbian couples need to apply recognition of parental status, and in practice, may use Reception of Oocytes from Partner (ROPA).
Gamete donation		
• Embryo	• Not allowed.	• Spare embryos can be donated by patients. • Embryos can be produced by composing donor gametes.
• Eggs	• Patient or unmarried donors, with no transmissible hereditary or infectious diseases. • Married donor if approved by husband and the recipient. • 21-35 years of age. • Up to 3 egg retrieval cycles.	• Any donor, with no transmissible hereditary or infectious diseases. • Older than 18. • Not more than 6 children from each donor. • Once in 3 months. • Rewarded 900-1000 €.

	• Once in 6 months. • From each cycle eggs donated to up to 3 recipients. • Rewarded from 2,450 € (for a patient-donor) to 4,900 €. • Subject to committee decision between a lesbian couple or any non-anonymous donation.	
• Sperm	• Unmarried donors, with no transmissible hereditary or infectious diseases. • 18-30 years of age. • Number of donations is decided by the bank manager. • Payment of approximately 60 €.	• Any donor, with no transmissible hereditary or infectious diseases. • Older than 18 • Not more than 6 children from each donor. • Payment of approximately 60 €.
Prenatal Genetic Diagnosis/Screening	A wide range of severe, high penetrance monogenetic diseases, with early onset and no cure (and also some later onset diseases such as Huntington and hereditary cancers).	
• PGD	• Similar conditions as for IVF. • A few private clinics treat wider range of diseases than public funded PGD. • Sex selection allowed for families with 4 children of same sex and pressing reason.	• Similar conditions as for IVF. • Requires authorization by CNRHA, case by case. • Sex selection is prohibited.
• PGS	PGS is allowed privately when there is a concern for structural or numerical maternal or paternal chromosomal abnormality.	
Gestational Surrogacy	• Couples (heterosexual) or single women with medical limitation to conceive. • A highly regulated procedure, each contract is subject for approval of a committee. • Remuneration is legal	• Illegal in Spain, any contract signed for this purpose is null.
Fertility preservation	When gametes or embryos are already preserved, number of children is unlimited.	
• Elective fertility preservation	• Women: age 30-41. Limited to 4 cycles or 20 eggs. Men: no limitations	• No defined age limit
Direct public support		
Publicly funding IVF		• Differs across regions.
• Marital status and sexual orientation	• Couples (heterosexual) or single women	• Couples (including lesbians) or single women
• Age	• Women 18-44	• Women 18-40, Men 18-55

• With Donor-egg	• Women up to 54 with medical justification. • Participation fee of approximately 2,450 € per donation.	• Women up to 40 with premature clinical ovarian failure established before the age 36.
• Number of cycles	• If 4 cycles resulted with no embryo implantation or 8 cycles resulted in no pregnancy, the continuation would depend on the HMO decision. • Up to 3 treatments with no embryo implantation for women older than 42 years (based on medical guidelines that vary from time to time).	• Up to 3 cycles per patient. • If a cycle failed, the patient is back to the waiting list.
• Number of Children	• Patient with less than two children with her current partner, or additional health insurance by the HMO for a third child.	• Patients with no children with their current partner. • Patients who already have children but hold frozen embryos from previous treatments.
• Publicly funded PGD	• A wide range of severe, high penetrance monogenetic diseases, with different levels of onset with no cure.	• Very limited, coverage differs across regions.
• Fertility Preservation for medical reasons (Men and Women)	• Fully covered up to a 2nd child.	• Partially publicly funded, when couples or single are childless.
Activity Registry	• Annual activity reports by the Health Ministry. Very limited character.	• National registry by law (1988), obliges all clinics to participate. • Until 2015 the registry carried out by the Spanish Society of Fertility (SEF), had a voluntary character and partial participation. • Participation is compulsory and since 2015 data covers most activity.
Donors Registries		
• Anonymity	• Donor identity is not revealed.	• Medical history and genetic information could be revealed to the born child and parents. • Donor identity may be revealed only if the descendant is under life risking conditions.
• Egg-donors registration	• By the Health Ministry - Registry of egg Donations. • By the Ministry of Justice - Registry of children born of egg donation.	• Each clinic (no centralization)

• Sperm-donors registration	• By the sperm banks (centralized by one bank).	• Each clinic (no centralization)

Source: own elaboration based on SEF (2015), Israel Ministry of Health, Boada et al., (2003) and personal interviews.

In Israel, the Health Ministry is occasionally advised by nominated committees regarding new legislation, while Health Maintenance Organizations (HMOs) and hospitals maintain certain autonomy by regularly dealing with enforcement and resource distribution. In contrast, in Spain legislation is advised by the National Committee of Human Assisted Reproduction (CNRHA), consists of 25 members appointed by different Ministries, scientific societies, and social organizations (Boada et al., 2003). The CNRHA is responsible for updating the law, evaluating research projects, and authorizing procedures of controversial nature.

Eligibility criteria in Spain are less strict, what could be partially linked to the fact that private entities hold most of the IVF market and gamete banks and are also actively involved in the regulatory process (as members of CNRHA). In Israel, limitations (by law) on private centers are stricter as almost all treatments are publicly funded, although more than 50% are provided by private clinics (State Comptroller, 2012; Kol et al., 2016).

Gamete donations in Spain are regulated and strictly anonymous, and although marketed as "altruistic", donations are entitled to a significant compensation rate and are being recruited by various means of advertisements. Thus, the local market for egg donations is among the largest in the world, and also an important destination for reproductive tourism (Bergmann, 2011; SEF, 2016; ESHRE, 2018). Conversely, in Israel, the ovum-donation law from 2010 is more restrictive. It enables almost only non-married women to donate and disqualifies cross-religion donations, thus attributing importance to the genetic/religious/racial make-up of the donated egg (Gruenbaum et al., 2011; Nahman, 2013). In practice, local egg donations are scarce, they mostly arrive from other ART patients (married or not), and the shortage is supplemented by donations from abroad, usually by non-Jewish donors (Birenbaum-Carmeli, 2016).

Both countries are relatively open towards the use of PGD. In Israel, it is more generously publicly covered, and the approach is more permissive towards late-onset diseases. In both countries, PGS is privately funded, since only a modest advantage for employing it has been perceived so far.

Surrogacy is illegal in Spain, but cross-border surrogacy is practiced by Spaniards. In contrast, Israel was among the first countries taken steps to legalize surrogacy (Teman, 2010; Shalev & Hashiloni-Dolev, 2011). However, it is not publicly funded and is significantly restricted, particularly for gay Israeli male couples, whose only option is to seek cross-border surrogacy. Overall, according to the Israeli Health Ministry, between 1996 and 2017, 1,458 cases were filled for the committee approval, and

between 1998 and 2017, 823 children were born by gestational surrogacy in Israel. Also, between 2005 and 2017, 1,513 requests to register children born through cross-border surrogacy were filled.

Fertility preservation for medical reasons is more generously funded in Israel. However, regarding elective fertility preservation, it is more liberally handled and less restricted in Spain.

Public insurance in Israel covers the vast majority of IVF cycles, while in Spain about 80% of cycles were provided by private clinics in 2016, with less than 20% publicly funded (SEF, 2016). It is a direct result of eligibility criteria for public funding, as described in Table 3.

In the last few years, activity registry in Spain is becoming more comprehensive and more reliable (according to the registry editors), following European and American standards. Conversely, Israel lacks a complete registry of activity. Donor registries in Israel are centralized, while Spanish donor registries are regionally managed since its national health service is highly decentralized. For both countries, there seem to be significant gaps between the legal requirements and actual implementation of registries, and the information is not organized in a way which facilitates detection of donors and follow-up by the different centers.

3.4. The Delphi survey

In order to delve further into the comparative analysis of ART regulatory approaches in Spain and Israel, we applied a Delphi survey combined with in-depth interviews, addressing two groups of experts.

3.4.1 Method

The experts' selection and the development of a questionnaire are key issues in Delphi analysis (Salazar-Elena et al., 2016). We selected the experts by trying to emulate an authentic bioethics committee for each country. Members were selected based on their skills, experience, and unique contribution to public discourse, without political interference or bias (Lock, 1990). For this purpose, we began by consulting members' lists of the Spanish bioethics committee, and the latest (2012) government appointed Israeli "Mor-Yosef" committee (in Israel advisory committees are occasionally appointed). We were assisted by an experienced member of the advisory board at the Spanish health ministry and by the coordinator of the "Mor-Yosef" committee, who guided us and provided some relevant contacts. In order to approach different perspectives on ART regulation, we selected experts of a multidisciplinary character, who have interest in ethical issues, whose careers were dedicated to ART from the fields of medicine, public health, law, ethics, philosophy, theology, sociology, economics or psychology (Bagheri et al., 2016; Gomes de Oliveira et al., 2017). We also aimed to balance the panels' composition between countries to enhance the comparability of the results. The two final

panels included 18 Israelis (12 women and 6 men) and 18 Spaniards (9 women and 9 men), as shown in Table 4.

Table 4. Distribution of panel members, by country and area of specialization

Professional Activity	Israel (18)		Spain (18)	
Doctors and Health departments directors	(5)	• Genetics (2) • Gynecology (3)	(7)	• Genetics and Biology (2) • Gynecology (5)
Civil servants in Health Administration	(3)	• Health system administration (2) • Jewish Law (1)	(2)	• Medicine and Health system administration • Law, Bioethics
Academic researchers	(6)	• Philosophy • Law • Bioethics (2) • Economics • Epidemiology	(7)	• Law and philosophy • Law and Bioethics • Bioethics (2) • Economics • Biology (2)
Psychologists and Social Workers	(2)	• Psychology • Social Work	(1)	• Psychology
Others	(2)	• Rabbi • Journalist	(1)	• Law and Bioethics (bioethics foundation)

A set of 27 in-depth semi-structured personal interviews lasting one hour on average were conducted. Preliminary interviews guide the design of the Delphi questionnaire and also enrich the analysis with more qualitative insights. In total 19 Israelis and 10 Spaniards were interviewed (from which 15 Israelis and 9 Spaniards also participated in the survey, together with an additional three Israelis and nine Spaniards who were not interviewed in person).

The Delphi survey was based on three groups of 10-point scale questions about a) the impact (both perceived and desirable) of different factors on ART regulation; b) experts' satisfaction with the way different aspects of ART provision are regulated; and c) their level of support for different policy measures to prevent infertility. We discussed and tested the first template during the last personal interviews in Spain and tested the final version with two Israeli experts. The survey was delivered in two rounds, the first between April and September 2018, and the second between September and December 2018. For the second round, we returned to each participant only regarding those questions for which consensus, proxied by the standard deviation (SD), was not reached (SD>2) (Landeta et al., 2008). For each expert we marked only those answers which were out of the interquartile range, allowing them to change replies and provide additional comments regarding their differed positions, in order to explain dissensus (Landeta & Barrutia, 2011) and draw different scenarios (Okoli & Pawlowski, 2004). Only one expert did not participate in the second round.

The statistical analysis was complemented with qualitative insights gathered through personal interviews and open comments from both Delphi rounds, which were essential in shaping the analysis and explain the experts' consensus and dissensus.

3.4.2. Key factors affecting regulations

The experts were asked to rate the optimal level of influence of ten key factors affecting regulations and to rate their actual impact according to their perception. Table 5 summarizes the experts' answers and contains a "Delta", which represents the difference between the "optimal" levels of influence that each factor should have according to the experts' opinion, and their mean perception of how the levels of impact really are. A positive Delta indicates that a factor is perceived as having a more significant impact than it should have, while a negative Delta suggests that a factor does not have enough impact compared to the optimal. Delta values close to zero would indicate that the actual impact is close to the optimal, representing the experts' contentment with the current situation. The table is ordered according to the four public interests introduced in section 2.2.

Table 5. Actual vs. optimal influence of different factors on ART regulations

1 – Very low impact to 10 – Very high impact			Israel		Spain	
			Mean	SD	Mean	SD
Health	a. Patient's health, clinical safety.	Actual	6.3	1.53	7.6	1.46
		Optimal	9.6	0.78	9.4	1.04
		Delta	-3.2	1.35	-1.8	1.32
	b. Scientific evidence for the success rates of the treatments.	Actual	6.0	1.87	5.9	1.80
		Optimal	9.1	0.94	9.2	1.04
		Delta	-3.1	1.91	-3.3	1.95
	c. Global trends and guidelines of regulatory agencies and scientific societies.	Actual	6.1	1.69	5.8	1.92
		Optimal	8.5	1.62	7.8	1.86
		Delta	-2.4	2.50	-2.0	1.78
Economic	d. Budgetary constraints of healthcare system.	Actual	5.1	2.93	7.5	2.04
		Optimal	6.3	1.93	5.9	2.54
		Delta	-1.2	3.36	1.6	3.22
	e. Freedom of commercial activities and the private sector's interest.	Actual	6.4	1.97	7.1	2.01
		Optimal	3.1	1.43	4.1	2.30
		Delta	3.3	2.14	3.0	2.69
Ethical	f. Protect vulnerable individuals from exploitation.	Actual	6.4	1.92	6.9	2.75
		Optimal	9.7	0.59	9.2	1.38
		Delta	-3.3	1.79	-2.2	1.94
	g. Patients' autonomy to make their own choices.	Actual	6.4	1.80	6.8	1.89
		Optimal	8.8	1.40	8.7	1.32
		Delta	-2.4	2.15	-1.9	1.71
Socio-Political	h. Equity of access	Actual	7.0	1.80	5.5	1.92
		Optimal	9.7	0.49	9.0	1.24
		Delta	-2.7	1.76	-3.5	2.01
	i. Public values and perceptions.	Actual	7.7	1.99	6.4	1.46
		Optimal	6.0	1.90	8.1	1.98
		Delta	1.7	3.03	-1.7	2.14
	j. National fertility rates.	Actual	6.7	1.18	5.5	2.26
		Optimal	4.6	2.32	7.8	2.60
		Delta	1.9	2.49	-2.3	1.88

We begin by highlighting the high degree of consensus for most answers in both panels (SD<2). For Israeli experts, a disagreement was only observable regarding the actual and optimal influence of the budgetary constraints and national fertility rates, respectively. The controversy was, in general, somewhat higher among the Spanish experts, particularly with respect to the role played by the

protection of vulnerable individuals, but also regarding the weight (actual and optimal) of private sector's interest and the national fertility rates.

Focusing on the Delta, according to both panels, health interest should have more impact on ART regulations. According to interviews and comments, current practices of ART in both countries fail to pay enough attention to scientific evidence and global trends of regulations. Many patients are undergoing an excessive number of treatments, particularly at an advanced age, when prospects for success are low. In Israel, it may be due to public funding policy, which encourages doctors and patients to keep attempting cycles with patients' own eggs until the age of 44. In the Spanish case, it was claimed that in private clinics "*the number of cycles performed is excessive and treatment may last as long as patients may pay"*, and that *"in the absence of an age limit some clinics offer donor-egg cycles to patients older than 50"*. Both panels repeatedly mentioned the risks derived from implanting more than one embryo. When comparing Israel and Spain to other countries, the number of embryos transferred after IVF as well as the share of multiple births are not unusually high, aside of a handful of European countries where lower rates of transfer are reported.

Regarding economic factors, both panels believed that private interests have an excessive impact on regulations. Many Spanish experts criticized the excessive involvement of private stakeholders in the regulatory agency CNRHA, and their efforts to eliminate limitations on private clinics and donor banks. Several Spanish respondents stressed the need to reduce the impact of commercial interest on regulations in favor of a more scientific approach. Moreover, Israelis claimed that many doctors in key roles are ignoring evidence that should lead to policy changes, when it is against their interest, and that *"private clinics are practicing cream skimming"*, i.e., doctors operate simultaneously in public and private clinics and send "hard patients" to private clinics where more substantial profits are generated.

Conversely, some experts from both panels also emphasized the *"importance of a private ART sector which absorbs most of the treatments"*, and underlined doctors' role, as described by one comment, *"alongside their economic interest, they are ultimate professionals, their knowledge and experience are valuable for appropriate regulations".* An additional thought-provoking comment by a panelist regarding ART physicians' role was that *"they affect public opinion through the media, participate in professional committees and are manning the health ministry".* It was, therefore, suggested that despite a conflict of interest, physicians should participate in the regulatory process, but not dominate it.

The Spanish panel believed that budgetary constraints have an excessive impact on regulatory decisions. In contrast, the Israeli panel claimed that repeated cycles for women of advanced age, *"are*

draining public funds which could be directed toward more effective procedures and this constitutes a burden on public clinics which otherwise could better address demand".

Under these conditions, both panels are preoccupied with low attention to ethical interests, expressed by insufficient protection of vulnerable individuals from exploitation. Moreover, according to the survey, both panels stated that patients should have more autonomy in decision-making, which they suggested to enable by better informing the patients regarding all possible approaches to treatment.

Finally, regarding socio-political interest, the Israeli panel stressed that national fertility and public values have an excessive impact over regulations, while the Spanish panel would have preferred more impact by these two factors. Dissatisfaction with the impact of the factor "equity of access", could be easily explained for Spain where *"long waiting lists in public clinics incentivize patients to approach private clinics"*. However, in Israel, cycles with one's own-eggs are more equally distributed while inequity arises regarding egg-donations and surrogacy.

3.4.3. Regulatory views

The panels were asked to rate their level of satisfaction with outcomes of regulations regarding ten categories. Results are displayed in Table 6, which shows the mean and standard deviation of each panel answers concerning each category. Mean values below 6 are interpreted as indicative of a low level of satisfaction.

Table 6. Satisfaction with outcome from regulation

1 - Very unsatisfied to 10 – Very Satisfied	**Israel**		**Spain**	
	Mean	**SD**	**Mean**	**SD**
a. Clinics' good practices, safety, proper diagnosis etc.	7.7	1.11	7.2	1.44
b. Preimplantation Genetic Diagnosis (PGD).	7.3	2.02	6.7	2.57
c. Anonymity of gametes and embryo donors.	6.2	2.97	7.5	2.65
d. Limitations on private clinics providing services.	5.9	2.13	6.6	2.38
e. Eligibility criteria for public funding of IVF.	6.1	2.16	5.4	1.95
f. Eggs-vitrification for elective egg preservation.	5.7	1.88	5.8	2.75
g. Public clinics' capacity to respond to the demand.	6.9	1.83	4.6	1.88
h. The regulations on reimbursements for gametes.	6.1	1.79	5.2	2.88
i. Gestational Carriers / Surrogacy.	6.1	2.08	3.2	2.50
j. Registry of gametes and embryos donors.	4.6	2.31	3.1	2.36

Again, the degree of consensus was lower among the Spanish experts, who generally were less satisfied with regulations (a low level of satisfaction may be observed for six out of the ten aspects included in the questionnaire). However, for the Israeli panel, a low level of satisfaction was only shown for regulations regarding limitations on private clinics providing services, eggs-vitrification for elective egg preservation and registry of gametes and embryos donors. We may notice that both panels were reasonably satisfied with good practices and clinical safety.

The Israeli panel was more satisfied with PGD, while Spanish experts were generally more critical concerning the use of PGS as we learned from comments. One expert described it as *"instrumentalization of IVF by adding techniques, which are not always necessary and may be introduced merely to increase economic gains"*.

Both panels were reasonably satisfied with the anonymity of gamete donors, particularly the Spanish panel. According to one Israeli expert: *"lack of access to parents' genetic material and medical history may constitute a discriminatory factor, by reducing one's chance to be cured of several conditions"*. She also claimed that *"given the donor's genetic information, it will be quite easy to detect his/her civil identity"*.

While the Israeli panel rated lower satisfaction with limitations on private services, according to comments and interviews, both panels endorsed more strict limits on cycles in private clinics concerning age, number of attempts, and securing a proper diagnosis. Moreover, the problem of enforcement was mainly raised in Spain, where one expert complained about the fact that *"private clinics face no real limits in the application of any of the techniques, whether they are permitted by law or not".*

Regarding direct public support, Spanish experts were unsatisfied with clinics' capacity to respond to the demand and with eligibility criteria for public services. They were generally in favor of increasing public provision of IVF cycles, and also favored the inclusion of coverage of egg donations and gamete banks in public health insurance.

Israelis were more satisfied overall with public funding, but advocated, both in interviews and by comments to reduce public funding of cycles performed for patients with their own eggs by lowering the age limit and limiting the number of cycles allowed. According to one expert: *"Comprehensive public coverage of ART derives from the Israeli social-ethos, which emphasizes the role of procreation, technology, and medicine"*. This policy may achieve low levels of inequality; however, it also creates a norm where women of advanced age are expected to be able to give birth to a genetically related child, hence *"pressuring women to keep trying cycles with their own eggs when prospects are low",*

according to another expert. Conversely, the Israeli panel was in favor of increasing public funding for patients with two children or more.

Both panels were preoccupied with existing regulations of elective fertility preservation which allows its practice. It was claimed that funding preservation might motivate women to use it, which is medically problematic. Moreover, several interviewees pointed out that if the technology is already being used, it should at least be done at an early age to achieve useful results.

The use of donor-eggs is a standard solution to age-related infertility in Spain, where although reimbursement for donation is much lower than in Israel, the market is very active, as it exceeds the minimum wage. Spanish experts were unsatisfied with this situation, advocating the reduction of reimbursement, as they were fearful of donors' exploitation. It was stated that in the absence of supervision and restrictions, private egg banks are gaining disproportionate profits from donations. By way of contrast, donor-eggs are scarce in Israel, and experts were in favor of increasing rewards for egg donations to increase the currently minimal supply.

The Spanish panel was extremely unsatisfied with regulations about surrogacy since prohibition does not prevent private companies from offering services abroad, which raises inequality in access and difficulties regarding child registration. A consensus was not reached concerning the correct solution; however, many suggested that the subject should be revised.

Finally, both panels were mostly unsatisfied with donor registries, underlining the gap between law and enforcement. In Spain, several experts claimed that *"some CNRHA members with vested interest disrupt the efforts to establish a national donor registry"*, but *"it will finally be launched soon, after numerous delays"*. Nevertheless, in the absence of registries, *"donors may donate more frequently than allowed, and it is difficult to exclude donors with hereditary genetic diseases"*. Strong dissatisfaction with the lack of proper activity registry in Israel was raised in personal interviews.

3.4.4. Views on alternative approaches to prevent and cure infertility

During interviews, experts raised different solutions that could be adopted to address increasing infertility and demand for IVF. Participants in the Delphi survey were asked to rate those measures, and the results are presented in Table 7, which displays the mean answers and standard deviation of each panel concerning each category.

Table 7. Measures to prevent and cure infertility

1 – From strongly opposed (0) to strongly support (10)	Israel		Spain	
	Mean	SD	Mean	SD
a. Distributing accurate information regarding age implication and environmental factors on infertility and success rates of assisted reproductive medicine (ART) via public-health campaigns in the educational system, thru family doctors and the media.	8.7	1.46	8.6	1.87
b. Securing proper diagnosis of infertility before referring to IVF.	8.7	1.18	8.5	1.97
c. Dedicating more resources to reduce environmental factors and cure/prevent diseases causing infertility.	7.4	2.12	8.4	2.21
d. Funding more research regarding environmental causes of infertility.	7.7	1.84	8.1	1.89
e. Increasing the supply and/or efficiency of publicly provided IVF to reduce waiting lists and inequity.	7.3	3.06	8.1	2.44
f. Increasing social support policies to facilitate parenting at younger age.	5.7	2.44	9.1	1.48
g. Funding (fully or partially) fertility preservation by freezing gametes.	5.7	2.72	7.7	3.11
h. Funding donor-eggs to increase supply.	6.9	1.95	5.6	3.18
i. The public sector should minimize its intervention in this issue.	2.6	1.42	2.9	3.07

expert groups highly supported securing the proper diagnosis of infertility, distributing more information regarding causes and success rates of ART, and dedicating more resources to detect environmental factors, prevent and cure infertility. However, experts also claimed that research is slow, complex, and uncertain.

The Spanish panel attributed the highest score to increasing social support policies for young parents, while the Israelis ranked it relatively low as they were satisfied with current child support policy. Some experts stressed that social policies should enable parenting at a young age, but not incentivize it.

Additionally, the Spanish panel had stronger support for funding fertility preservation, while the Israelis preferred funding more egg donations, considering their shortfall in Israel.

Finally, it was evident from the answers that both panels would not recommend minimizing the intervention of the public sector and leaving the solution in the hands of the private sector. One key element raising from interviews and the survey is that the experts support prevention more than further treatment, and their comments emphasized non-medical solutions, such as social support, education, and facilitating adoption. As stated by a Spanish expert: *"People with fertility problems are too easily directed to IVF. Research regarding infertility causes should be enhanced, and it would be*

necessary to investigate what are the specific causes of infertility regarding every single person who visits the gynecologist, before sending her to IVF".

3.5. Discussion

This comparative study is useful to better understand the similarities and differences between ART regulations in Spain and Israel, those factors influencing each regulatory framework, as well as their strengths and deficiencies.

Both countries are among the heaviest users of ART, due in large part to age-related infertility. In Spain, 35% of IVF cycles in 2016 were performed on women older than 40, of which about 56% were done with donor-eggs (SEF, 2016). Moreover, in Israel, IVF cycles for this age group count for more than 40%, although with a much lower percentage using donor-egg (Kol et al., 2016). However, this phenomenon may be explained by different reasons in each of these countries. In Spain, it follows a tendency to postpone parenthood, which is due to unfavorable work hours, gender inequality, low wages, job instability, and limited policy support among other socio-financial reasons (Bravo-Moreno, 2017; Lopez-Rodriguez, 2017; Marre et al., 2018). Whereas in Israel, cultural, political and social environments are shaping public views on infertility, ART and genetic relatedness. Thus, Israelis expect to have large families and are committed to repeat many IVF cycles in their advanced reproductive age, in order to give birth to a genetically related child (Birenbaum-Carmeli & Dirnfeld, 2008; Birenbaum-Carmeli, 2010).

The increased demand for ART comes with several costs, and our Delphi panels were dissatisfied with some regulatory aspects. An insufficient response by the public health system, as marked by the Spanish panel, means that the majority of the couples turn to the private market where the treatments cast a heavy financial burden, which also creates unequal access to services. Spain is also characterized by extensive use of donor-eggs, which has been clinically very efficient (SEF, 2016; CDC, 2018). However, as stated by some Spanish experts and as discussed by Bergmann, (2011), extending the reproductive age by using gametes from young donors provides only a partial solution, far from optimal and with important social implications that should be carefully addressed. In 2014, Spain accounted for 54% of the received egg donations reported in Europe (ESHRE, 2018), and in the last reported year (2016), 14,747 donor cycles were initiated involving thousands of donors, providing more than 9,000 children who account for 28% of total IVF births (SEF, 2016).

The magnitude of this phenomenon emphasizes health and social risks to egg donors and raises questions regarding the anonymity of donations and the regulations on reimbursement. The current

financial compensation is high enough to motivate a large number of young Spanish women to donate their eggs, but it also may be considered that their "*reproductive labor*" is poorly paid (Marre et al., 2018), particularly compared with the profit pocketed by intermediaries. Interestingly, some of the experts suggested reducing this reimbursement, but the consequences derived from such action, as well as its justification in moral terms, should be very carefully tested and publicly discussed.

In contrast, Israel has more comprehensive public funding, leading to more equality in access to IVF treatments. However, techno-scientific expectations (Borup et al., 2006) lead patients of advanced age to repeat many cycles using their own eggs with a priori low prospects (Kol et al., 2016), which expose them to physical, emotional and financial risks, while spending valuable public resources. The Israeli panel favored a change in the current policy but was also aware of the political-cultural difficulties in implementing such change. Egg donations, as an alternative solution carries a significant complexity of a political-religious nature. Many Israelis hold a conservative approach to egg donations, due to various reasons, including the risk of inadvertent consanguineous marriage, contradictory attitudes towards religious affiliation of the child and the need for conversion, the high importance attributed to having a genetically related child, and the preoccupation with donor's genotype (Nahman, 2013). In practice, donations produced in Israel are limited, and most donor-eggs arrive from abroad which casts a financial burden on patients. It remains an option of last resort, after failing many IVF cycles.

A shared weakness in both countries is the registration of gamete donations, which gained the lowest level of satisfaction by both panels. The size of the Spanish gamete market stresses the importance of central and comprehensive registries, while the fact that in Israel most egg donations arrive from abroad emphasizes the difficulty to implement such a task. In the absence of proper registries, within a few decades hundreds of thousands of children would have no access to one or both of their parents' genetic information and would be unaware of their genetically related siblings. This would confront them with various disadvantages considering the importance of family medical history for developing preventive conducts, the risk of consanguineous relationships (Sobotka, 2016), and the potential of family-based exome and germlines sequencing among other methods (Kuhlen, et al., 2019; Patowary et al., 2019).

Although a marginal niche in quantitative terms, gestational surrogacy is among the most contested issues in ART. While the Israelis were more settled with its current regulation, it raised visible dissatisfaction among the Spanish panel. However, both panels stressed the limitations of national regulations due to the cross-border option, which proves the weakness of absolute prohibition as applied in Spain, or as applied in Israel concerning gay Israeli male couples. With the

absence of social consent and inability to achieve political consensus, surrogacy becomes a grey-zone, where some illegal acts may be practiced, and then a posteriori acknowledged.

In light of the growing demand for ART, both panels emphasized the importance of promoting alternatives to the medicalization of reproduction. Some possible measures equally supported by both expert groups were related to the observation that ART is often perceived as a solution to age-related infertility and a way to postpone parenthood. The risk of this perception is also emphasized in other studies (Hashiloni-Dolev et al., 2011; García et al., 2017). The experts in our panels tend to favor a more effective distribution of accurate information regarding both ART and infertility, through different available means. They also emphasized the importance of epidemiological research on infertility and the need to focus on its prevention instead of relying on the medical solution. The Spanish experts were particularly interested in the social solution, i.e., to facilitate parenting in young age via welfare policies, which already prevail in Israel. The rising solution of fertility preservation was handled very cautiously by both panels. The Spaniards supported it more strongly than the Israeli experts, but both groups stressed that regulations in this field should be revised, particularly regarding age limits. According to the experts consulted, preserving eggs after the age of 35 is less effective and, if at all, it should be done earlier, following the provision of comprehensive information and accompanied by a broad and open societal debate.

Finally, regarding the factors influencing regulatory decisions, both panels were discontent with the high impact of the private sector and its commercial interest, which comes hand in hand with their perception, of weak health interest and social justice. This regulatory imbalance and the lack of enforcement result in excessive numbers of IVF cycles, as well as the “push” of treatment add-ons such as PGS, even though its benefit to treatment is yet unclear. It brings to our attention the principal-agent problem, since asymmetric information in this context may potentially lead to supplier-induced demand, whereby physicians in pursuit of monetary profits treat patients beyond the point from which they might actually benefit (Cutler et al., 2017).

Given that the regulation of ART is a broad field, our analysis is centered around the most significant findings brought up by the experts, whose focus, as we recall, also guided the design of the Delphi survey. Hence, beyond being dependent on experts’ willingness to participate, a Delphi panel selection always has a certain level of subjectivity. Different experts may have different focuses and attitudes. Moreover, although our selection of two countries with very pro-ART attitudes has advantages, it is also limiting. Further studies presenting different arguments from different cultural contexts would enrich this discussion.

3.6. Conclusions

A key contribution of this paper is the development of a comprehensive analytical framework which allows for any national comparisons of ART regulation. This framework identifies and categorizes the main components of ART regulations and also those factors that explain different regulatory choices. Hence, it may be a very useful tool for cross-country research.

Our empirical analysis, focused on two countries among the most intensive users of ART, yields some worth- noting conclusions. The main similarity between Israel and Spain is the increasing use of ART due to age-related infertility. Socio-financial conditions and techno-scientific expectations are leading many women and men to postpone parenthood, which has been described as "*structural infertility*" (Marre, 2009; Marre et al., 2018). The inadequacy of ART to solve such a problem, with the many challenges and undesired implications it carries, should be the subject of broader social debate. Our research points to some crucial issues which require further consideration, such as the financial and emotional burden on patients (and donors), justice and inequality in this market, the ethics of gamete donations, donor's anonymity and over-prescription.

The regulatory situation in Israel has been described by Shalev & Hashiloni-Dolev as a "*technocracy of official expert ethics committees, which controls life-and-death decisions*". It seems that many crucial decisions are decentralized and handled by such committees in hospitals and clinics and that "*experts are the legal and ethical gatekeepers of new technologies*" (Shalev & Hashiloni-Dolev, 2011, p. 160). Meanwhile, in Spain, the CNRHA holds strong commercial interests, as currently "*several members of the committee come from the most important private IVF centers in Spain*" (Pavone & Arias, 2012, p. 250), a statement which was strongly supported by the Spanish panel. Considering the regulatory deficiencies identified in this paper and the panels' evaluation of impact factors, both countries should consider the establishment of non-governmental statutory central regulatory agencies. Such kind of agencies devoid of commercial interest, with the representation of scientific societies of various fields, professional associations, consumer groups, and political-religious groups, would streamline the system and facilitate regulatory decisions.

Also, data collection and transparency could assist in the conduction of epidemiological studies and prevention, which may reduce the dependency on ART. In recent years, national activity registry by the Spanish Fertility Association (SEF) has advanced substantially, while in Israel such an initiative has been gaining momentum in recent years, but still without full results. Nevertheless, the SEF report, similar to reports by other leading ART industries, could be improved. Registries should include more details regarding clinical diagnosis, and could also separate between PGD from PGS, two emerging techniques with different aims, to facilitate the follow up of their development, including the analysis

of the contribution of PGS to IVF success rate. Additionally, it would be useful to have information about the economic dimension of ART, including average costs, disaggregated by type of provider (public and private), which is now absent from most reports.

In sum, our study draws attention to some controversial issues that would need to be addressed by regulators in the future. Given the expected technological progress in ART and its broad implications for humankind, further research and policy debates are necessary in order to engage in a more systematic regulatory foresight that may better guide government responses. As several authors claim (Blind, 2008; Garden and Winickoff, 2018), such regulatory debates and foresight exercises need to be open to a wide variety of stakeholders, including more balanced, transparent and systematic forms of public engagement to discuss how effective existing regulations are and how they should be adapted to deal with future applications of technology.

References:

Agarwal, A., Mulgund, A., Hamada, A., & Chyatte, M. R. (2015). A Unique View on Male Infertility Around the Globe. Reproductive Biology and Endocrinology, doi 10.1186/s12958-015-0032-1.

Aragona, C., Mohamed, A. M., Salomè B Espinola, M., Linari, A., Pecorini, F., Micara, G., & Sbracia, M. (2011). Clinical Complications after Transvaginal Oocyte Retrieval in 7,098 IVF Cycles. Fertility and Sterility, 95(1), 293-4. doi: 10.1016/j.fertnstert.2010.07.1054.

ASRM, P. C. (2015). Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility, 103(3), e18-25. doi: 10.1016/j.fertnstert.2014.12.103.

Batzer, F. R., & Ravitsky, V. (2009). Preimplantation Genetic Diagnosis: Ethical Considerations. In V. Ravitsky, A. Fiester, & A. L. Caplan, The Penn Center Guide to Bioethics. (pp. 339-354). New York: Springer .

Bergmann, S. (2011). Reproductive Agency and Projects: Germans Searching for Egg Donation in Spain and the Czech Republic. Reproductive BioMedicine Online, 23, 600– 608.

Bernal-Delgado et al. (2018). Health Systems in Transition - Spain - Health System Review. ISSN 1817-6127 Vol. 20 No. 2.

Bhatia, R., & Campo-Engelstein, L. (2018). A Comparative Analysis of European and Amercan Professional Ethics Opinions and USNEWS and Popular Media. Science, Technology, & Human Values, 43(5), 864-887, doi: 10.1177/0162243918754322.

Birenbaum-Carmeli, D. (2010). Genetic Relatedness and Family Formation in Israel: Lay Perceptions in the Light of State Policy. New Genetics and Society, 29, 1, 73–85, doi: 10.1080/14636770903561380.

Birenbaum-Carmeli, D. (2016). Thirty-five Years of Assisted Reproductive Technologies in Israel. Reproductive Biomedicine & Society Online, 2, 16-23, doi: org/10.1016/j.rbms.2016.05.004.

Birenbaum-Carmeli, D., & Dirnfeld, M. (2008). In Vitro Fertilisation Policy in Israel and Women's Perspectives: The More the Better? Reproductive health matters, 16(31):182–191, doi: 10.1016/S0968-8080(08)31352-4.

Blind, K. (2008). Regulatory Foresight: Methodologies and Selected Applications. Technological Forecasting & Social Change, 75, 496–516, doi: 10.1016/j.techfore.2008.02.004.

Boada, M., Veiga, A., & Barri, P. N. (2003). Spanish Regulations on Assisted Reproduction Techniques. Journal of Assisted Reproduction and Genetics, 20, 7, 271-275, doi: 10.1023/A:1024558404061.

Boivin, J., Bunting, L., A.Collins, J., & Nygren, K. G. (2007). International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. Human Reproduction, 22, 6, 1506–1512, doi: 10.1093/humrep/dem046.

Borup, M., Brown, N., Konrad, K., & Van Lente, H. (2006). The Sociology of Expectations in Science and Technology. Technology Analysis & Strategic Management, 18, 3/4, 285–298, doi: 10.1080=09537320600777002.

Bosser, R., Gispert, R., Torne, M., & Calaf, J. (2009). Status of Human Assisted Reproduction in Spain: Results from the New Registry of Catalonia. Reproductive BioMedicine Online; www.rbmonline.com/Article/4049 on web 22 September 2009, 19:5, 727–733, doi: 10.1016/j.rbmo.2009.09.004.

Bravo-Moreno, A. (2017). Politics, Doctors, Assisted Reproductive Technologies & Religion: Transgenerational Understandings and Experiences of Single Motherhood in Spain. Health Care for Women International, 38:10, 1058-1074, doi: 10.1080/07399332.2017.1360890.

Brigham, K. B., Cadier, B., & Chevreul, K. (2013). The Diversity of Regulation and Public Financing of IVF in Europe and Its Impact on Utilization. Human Reproduction, 3, 666-75. doi: 10.1093/humrep/des418.

CDC. (2018). Assisted Reproductive Technology - National Summary Report 2016. Atlanta, US,: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, https://www.cdc.gov/art/pdf/2016-report/ART-2016-National-Summary-Report.pdf.

Chambers, G. M. et al.,. (2014). The Impact of Consumer Affordability on Access to Assisted Reproductive Technologies and Embryo Transfer Practices: an International Analysis. Fertility and Sterility, 101(1), 191-198.e4, doi: 10.1016/j.fertnstert.2013.09.005.

Clements, C. A. (2009). What About the Children? A Call for Regulation of Assisted Reproductive Technology. Indiana Law Journal, 84(1), 331-352, http://www.repository.law.indiana.edu/ilj/vol84/iss1/7.

Cutler, D., Skinner, J. S., L., Stern, A. D., & Wennberg, D. (2019). Physician Beliefs and Patient Preferences: A New Look at Regional Variation in Health Care Spending. American Economic Journal: Economic Policy, 11(1) 192–221, doi: org/10.1257/pol.20150421.

Davis, L. B., Champion, S. J., Fair, S. O., Baker, V. L., & Garber, A. M. (2010). A Cost-Benefit Analysis of Preimplantation Genetic Diagnosis for Carrier Couples of Cystic Fibrosis. Fertility and Sterility, 93, 6, doi:10.1016/j.fertnstert.2008.12.053.

Dondorp, W., de Wert, G., Pennings, G., Shenfield, F., Devroey, P., Tarlatzis, B., . . . Diedrich, K. (2012). Oocyte Cryopreservation for Age-Related Fertility Loss. Human Reproduction, 5, 1231-7, doi: 10.1093/humrep/des029.

ESHRE. (2018). Assisted Reproductive Technology in Europe, 2014: Results Generated from European Registers by ESHRE. Human Reproduction, 33(9):1586–1601. doi: org/10.1093/humrep/dey242.

ESHRE Capri Workshop Group. (2014). Birth Defects and Congenital Health Risks in Children Conceived Through Assisted Reproduction Technology (ART): a Meeting Report. Journal of Assisted Reproduction and Genetics, 8, 947-58, doi: 10.1007/s10815-014-0255-7.

Fauser, B. C., P., D., Diedrich, K., B. B., Bonduelle, M., Delemarre-van de Waal, H. A., . . . Wells, D. (2014). Health Outcomes of Children Born After IVF/ICSI: a Review of Current Expert Opinion and Literature. Reproductive BioMedicine Online, 2, 162-82, doi: 10.1016/j.rbmo.2013.10.013.

Frith, L., & Blyth, E. (2014). Assisted reproductive technology in the USA: is more regulation needed? Reproductive BioMedicine Online, 29, 516–523, doi: org/10.1016/j.rbmo.2014.06.018.

García, D., Vassena, R., Prat, A., & Vernaeve, V. (2017). Poor Knowledge of Age-Related Fertility Decline and Assisted Reproduction Among Healthcare Professionals. Reproductive Biomedicine Online, 34, 1, 32-37, doi: org/10.1016/j.rbmo.2016.09.013.

Garden, H., & Winickoff, D. (2018/12, OECD Publishing, Paris). Gene editing for advanced therapies: Governance, policy and society. OECD Science, Technology and Industry Working Papers, https://doi.org/10.1787/8d39d84e-en.

Garland-Thomson, R. (2015). Human Biodiversity Conservation: A Consensual Ethical Principle. The American Journal of Bioethics, 15(6):13-5. doi: 10.1080/15265161.2015.1028663.

Gomes de Oliveira, M. C., A. d., & Nogueira-Martins, M. C. (2017). The Experience of the Bioethics Committee from a Public Hospital. Revista Bioetica, 25 (2): 338-47, doi: org/10.1590/1983-80422017252194.

Gruben, V. (2017). Freezing as Freedom? A Regulatory Approach To Elective Egg Freezing And Women's Reproductive Autonomy. Alberta Law Review, 54, 3, 753-774.

Gruenbaum, B. F., Pinchover, Z. S., Lunenfeld, E., & Jotkowitz, A. (2011). Ovum donation: examining the new Israeli law. European Journal of Obstetrics & Gynecology and Reproductive Biology, 159 40–42, doi: 10.1016/j.ejogrb.2011.07.011.

Habermas, J. (2003). The Future of Human Nature. Cambridge: The translation polity press.

Harmon, S. H. (2016). Modernizing Biomedical Regulation: Foresight and Values in the Promotion of Responsible Research and Innovation. Journal of Law and the Biosciences, 680–686, doi:10.1093/jlb/lsw053.

Hashiloni-Dolev, Y., & Weiner, N. (2008). New reproductive technologies, genetic counselling and the standing of the fetus: views from Germany and Israel. Sociology of Health & Illness, 30,7, 1055–1069, doi: 10.1111/j.1467-9566.2008.001105.x.

Hashiloni-Dolev, Y., Kaplan, A., & Shkedi-Rafid, S. (2011). The Fertility Myth: Israeli Students' Knowledge Regarding Age-Related Fertility Decline and Late Pregnancies in an Era of Assisted Reproduction Technology. Human Reproduction, 11, 3045-53, doi: 10.1093/humrep/der304.

Health Ministry of Israel. (2018). In Vitro Fertilization (IVF) Treatments 1990-2016. Israel: Facilities and Equipment Licensing Division, Health Information Division, https://www.health.gov.il/PublicationsFiles/IVF1990_2016.pdf.

Ho, M., et al. (2016). A Framework for Incorporating Patient Preferences Regarding Benefits and Risks Into Regulatory Assessment of Medical Technologies. . Value in Health, 19(6), 746-750.

Hofer, M. P., Jakobsson, C., Zafiropoulos, N., Vamvakas, S., Vetter, T., Regnstrom, J., & Hemmings, R. J. (2015). Regulatory Watch: Impact of Scientific Advice from the European Medicines Agency. The European Medicines Agency., 302-303, doi: 10.1038/nrd4621.

INE. (2018). Tasas de Paro por Distintos Grupos de Edad, Sexo y Comunidad Autónoma. http://www.ine.es/jaxiT3/Tabla.htm?t=1579.

Inhorn, M. C., & Patrizio, P. (2015). Infertility Around the Globe: New Thinking on Gender, Reproductive Technologies and Global Movements in the 21st Century. Human Reproduction Update, 21, 4, 411–426, doi: 10.1093/humupd/dmv016.

Jasanoff, S., & Metzler, I. (2018). Borderlands of Life: IVF Embryos and the Law in the United States, United Kingdom, and Germany. Science, Technology, & Human Values, 1-37, doi: 10.1177/0162243917753990.

Johnson, L. (2014). Regulation of Assisted Reproductive Treatment (ART) in Australia & Current Ethical Issues. Indian Journal of Medicine Research, 140, 9-12.

Johnson, M., & Petersen, K. (2008). Public Interest or Public Meddling? Towards an Sbjective Framework for the Regulation of Assisted Reproduction Technologies. Human Reproduction, 3, 716-28, doi: 10.1093/humrep/dem387.

Klitzman, R. (2008). Anticipating Issues Related to Increasing Preimplantation Genetic Diagnosis Use: a Research Agenda. Reproductive BioMedicine Online, 17, 1, 33-42, doi: 10.1016/S1472-6483(10)60188-5.

Knoepfler, P. (2016). GMO Sapiens, The Life-Changing Science of Designer Babies. Singapore: World Scientific Publishing.

Kol, S., Bergovoy, L., Yellin, Segal, Y., & Porath, A. (2016). In Vitro fertilization (IVF) treatments in Maccabi Healthcare Services 2007-2014. Israel Journal of Health Policy Research, 5:14, doi: 10.1186/s13584-016-0072-9.

Kuhlen, M., Taeubner, J., Brozou, T., Wieczorek, D., Siebert, R., & Borkhardt, A. (2019). Family-Based Germline Sequencing in Children with Cancer. Oncogene, 38, 1367–1380, do: org/10.1038/s41388-018-0520-9.

Landeta, J., & Barrutia, J. (2011). People Consultation to Construct the Future: A Delphi Application. International Journal of Forecasting, 27(1), 134–151, doi: .org/10.1016/j.ijforecast.2010.04.001.

Landeta, J., J., M., Ruíz, V., & Galter, J. (2008). Results of a Delphi Survey in Drawing Up the Input–Output Tables for Catalonia. Technological Forecasting & Social Change, 75(1), 32–56, doi: org/10.1016/j.techfore.2007.01.005.

Lemoine, M.-E., & Ravitsky, V. (2013). Toward a Public Health Approach to Infertility: The Ethical Dimensions of Infertility Prevention. Public Health Ethics, 1-15, doi:10.1093/phe/pht026.

Lemoine, M.-E., & Ravitsky, V. (2015). Sleepwalking Into Infertility: The Need for a Public Health Approach Toward Advanced Maternal Age. The American Journal of Bioethics, 15:11, 37-48. doi: 10.1080/15265161.2015.1088973.

Lock, S. (1990). Towards a National Bioethics Committee. British Medical Journal, 300, 1149-1150, doi: 10.1136/bmj.300.6733.1149.

Lopez-Rodriguez, S. (2017). Public Policies and the Production of Vulnerability Spaces. The Construction of the Woman-Mother in Spanish Political Discourse. Revista Española de Ciencia Política, 44, 97-120.

Marre, D. (2009). The silences of the Spanish Adoption. Revista de Antropología Social, 18 97-126, http://www.redalyc.org/articulo.oa?id=83817222006.

Marre, D., San Román, B., & Guerra, D. (2018). On Reproductive Work in Spain: Transnational Adoption, Egg Donation, Surrogacy. Medical Anthropology, 37, 2, 158–173, doi: org/10.1080/01459740.2017.1361947.

Martin, J. F. (2016). The National Bioethics Committees and the Universal Declaration on Bioethics and Human Rights: Their Potential and Optimal Functioning. In A. Bagheri, J. D. Moreno, & S. Semplici, Global Bioethics: The Impact of the UNESCO International Bioethics Committee (pp. 125-136). Springer International Publishing, doi: 10.1007/978-3-319-22650-7.

Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS Medicine, 9(12), e1001356. doi: 10.1371/journal.pmed.1001356.

Mayor, B., Casada, R. R., L. J., López-Gunn, E., & Villarroya, F. (2016). An Expert Outlook on Water Security and Water for Energy Trends to 2030–2050. Water Policy, 18 (1) 1-18; doi: 10.2166/wp.2015.196.

Melander, L. (2018). Scenario Development in Transport Studies: Methodological Considerations and Reflections on Delphi Studies. Futures, 96, 68–78, doi: org/10.1016/j.futures.2017.11.007.

Nahman, M. (2013). Extractions - An Ethnography of Reproductive Tourism. UK: Palgrave Macmillan.

Nelson, E. L. (2006). Comparative Perspectives on the Regulation of Assisted Reproductive Technologies in the United Kingdom and Canada. Alberta Law Review, 43, 4, 1023-1048.

Okoli, C., & Pawlowski, S. D. (2004). The Delphi Method as a Research Tool: an Example, Design Considerations and Applications. Information & Management, 42(1), 15–29, doi: 10.1016/j.im.2003.11.002.

Orvieto, R. (2013). Ovarian Hyperstimulation Syndrome- An Optimal Solution for an Unresolved Enigma. Journal of Ovarian Research, 6(1), 77, doi: 10.1186/1757-2215-6-77.

Patowary et al. (2019). Family-Based Exome Sequencing and Case-Control Analysis Implicate CEP41 as an ASD Gene. Translational Psychiatry, 9, 4, doi: org/10.1038/s41398-018-0343-z.

Pavone, V., & Arias, F. (2012). Beyond the Geneticization Thesis: The Political Economy of PGD/PGS in Spain. Science, Technology, & Human Values, 37(3) 235-261, doi: 10.1177/0162243911411195.

Pennings, G. (2009). International Evolution of Legislation and Guidelines in Medically Assisted Reproduction. Reproductive BioMedicine Online, 18 Suppl 2:15-8ת doi: 10.1016/S1472-6483(10)60443-9.

Pennings, G., de Mouzon, J., Shenfield, F., & Ferraretti, A. P. (2014). Socio-Demographic and Fertility-Related Characteristics and Motivations of Oocyte Donors in Eleven European Countries. Human Reproduction, 5, 1076–1089, doi: 10.1093/humrep/deu048.

Präg, P., & Mills, M. C. (2017). Assisted Reproductive Technology in Europe:Usage and Regulation in the Context of Cross-Border Reproductive Care. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 289-309). Berlin: Springer.

Ravitsky, V. (2017). The right to know one's genetic origins and cross-border medically assisted reproduction. Israel Journal of Health Policy Research, 6:3, doi: 10.1186/s13584-016-0125-0.

Rimon-Zarfaty, N., Raz, A. E., & Hashiloni-Dolev, Y. (2011). When does a Fetus Become a Person? An Israeli viewpoint. Journal of Family Planning and Reproductive Health Care, 37:216–224. doi: 10.1136/jfprhc-2011-0110.

Rogers, E. M. (1983). Diffusion of Innovation, Third Edition. New York: The Free Press.

Salazar-Elena, J. C., Sánchez, M., & Otamendi, F. (2016). A Non-Parametric Delphi Approach to Foster Innovation Policy Debate in Spain. Sustainability, 8, 487; doi: 10.3390/su8050487.

SEF. (2010). *Registro de la Sociedad Española de Fertilidad: Técnicas de Reproducción Asistida (IA y FIV/ICSI). Año 2.010.* https://www.registrosef.com/public/Docs/sef2010_IAFIV.pdf: Sociedad Espanola de Fertilidad.

SEF. (2016). Registro Nacional de Actividad - Técnicas de Reproducción Asistida, Informe estadístico de Técnicas de Reproducción Asistida 2016. https://www.registrosef.com/public/docs/sef2016_IAFIVm.pdf: Sociedad Española de Fertilidad.

Shalev, C., & Hashiloni-Dolev, Y. (2011). Bioethics Governance in Israel: an Expert Regime. Indian Journal of Medical Ethics, 8, 3, https://ijme.in/articles/bioethics-governance-in-israel-an-expert-regime/?galley=pdf.

Shalev, C., Moreno, A., Eyal, H., Leibel, M., Schuz, R., & Eldar-Geva, T. (2016). Ethics and Regulation of Inter-country Medically Assisted Reproduction: a call for Action. Israel Journal of Health Policy Research, 5:59, doi: 10.1186/s13584-016-0117-0.

Shulman, C., & Bostrom, N. (2014). Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer? Global Policy, 5(1) 85-92, doi: 10.1111/1758-5899.12123 .

Sobotka, T. (2016). Childlessness in Europe: Reconstructing Long-Term Trends Among Women Born in 1900–1972. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 17-50). Berlin: Springer Open.

Spar, L. D. (2006). The Baby Business, How Money Science, and Politics Drive the Commerce of Conception . Boston, Massachusetts: Harward Business School Press.

State Comptroller. (2012). In-Vitro Fertilization - Annual Report (63λ).

Teman, E. (2010). Surrogate Selves and Embodied Others. In Birthing a Mother: The Surrogate Body and the Pregnant Self. Berkeley; Los Angeles; London: University of California Press, 31-53, http://www.jstor.org/stable/10.1525/j.ctt1pngs3.8.

Von der Gracht, H. A. (2012). Consensus Measurement in Delphi Studies Review and Implications for Future Quality Assurance. Technological Forecasting & Social Change, 79(8), 1525–1536, doi: 10.1016/j.techfore.2012.04.013.

Wert D, G. e. (2014). ESHRETask Force on Ethics and Law 23: Medically Assisted Reproduction in Singles, Lesbian and Gay Couples, and Transsexual People. Human Reproduction, 29, 9, 1859–1865, doi:10.1093/humrep/deu183.

4. CONTESTING THE GENETICIZATION THESIS IN HUMAN REPRODUCTION:

INSIGHTS FROM ISRAEL AND SPAIN

4.1. Introduction

The birth of Louis Brown in 1978 was the first successful use of In-Vitro Fertilization (IVF) for human reproduction, following 30 years of attempts on extracted human eggs. Since then, IVF has remarkably improved, providing solutions to an increasing number of pathologies of infertility. In particular, IVF is increasingly complemented through embryo selection by Preimplantation Genetic Diagnosis (PGD), available since 1990. More recently, genetic engineering (GE) of human embryos by CRISPR/Cas has become practicable, although it remains at an experimental stage.

Long before these developments, in "Brave New World" (1932), Huxley had imagined a world where reproduction was mainly attained through Assisted Reproductive Technology (ART) due to the benefits associated with the selection and manipulation of embryos. Ever since, many other authors have developed this *geneticization thesis* and its implications for humankind (Ramsey, 1972; Silver, 1997; Greely, 2016). In this paper, we refer to the geneticization of reproduction as the process whereby the ability to select or design genetic traits of embryos in-vitro could turn IVF from a technical solution for infertility into the mainstream procedure for reproduction. The term geneticization was defined by Lippman as "an ongoing process by which differences between individuals are reduced to their DNA codes, with most disorders, behaviors and physiological variation defined, at least in part, as genetic in origin" (Lippman, 1991: p. 19).

Common speculation in the bioethics literature discusses the possibility that, at some point, the qualities of genetically selected or engineered persons will surpass those of naturally conceived ones, which would motivate a regular use of reproductive genetics (Greely, The End of Sex and the Future of Human Reproduction, 2016; Knoepfler, 2016; Nuffield Council on Bioethics, 2018). Such a scenario can be identified as the consequence of a "technology-push" diffusion trajectory of ART (Nemet, 2009), resulting from "a moment of breakthrough" (Brown & Michael, 2003).

However, in this paper, we depart from technological determinism or breakthrough perspectives and emphasize instead that technology and the social environment influence each other reciprocally in an extended process, shaped by the evolution of technological momentum and social values over time (Bijker et al., 1987; Brown & Michael, 2003; Nuffield Council on Bioethics, 2018). Indeed, the literature on technological change emphasizes that the process of innovation is not linear but interactive, as the technology and its users affect each other along the way (Walsh, 1983; Nemet,

2009; Peters et al., 2012; Di Stefano et al., 2012). Therefore, we approach the diffusion of ART complementing the "technology-push" approach with a "demand-pull" perspective that underscores the importance of socio-technical imaginaries and pays particular attention to the role played by the regulatory framework (Nemet, 2009).

This paper reconsiders the viability of the geneticization thesis in human reproduction and attempts to contribute to the ethical discussion concerning ART, which holds important implications for regulation. We contribute to this agenda by critically analyzing the diffusion trajectories of ART and collecting key-informants' views concerning the regulation of reproductive genetics through a series of in-depth interviews and Delphi surveys with panels of experts from two leading countries in the field of ART, Israel and Spain.

Delphi is a widely used qualitative method for forecasting, assessment and decision making regarding complex problems, built on a panel of experts who contribute with their knowledge and experience (Landeta et al., 2008; Salazar-Elena et al., 2016). It is conducted with controlled feedback following a two-rounds survey, which allows experts to change their replies or add comments after learning the general views (Landeta & Barrutia, 2011; Von der Gracht, 2012; Mayor et al., 2016). Our Delphi panels included experts from various ART-related fields and aimed to simulate typical bioethics committees used to advise regulatory processes.

Israel and Spain constitute a relevant empirical setting since these countries have among the most active ART industries in the world. In 2014, Spain was practicing the largest number of IVF cycles in Europe and a third of the continent's PGD procedures (ESHRE, 2018), and Israel had the highest number of IVF cycles worldwide in relative terms (Health Ministry of Israel, 2018)**.** Both countries have supportive attitudes towards reproductive genetics, leading them to conduct venturesome PGD practices (Pavone & Arias, 2012; Zlotogora, 2014; Zuckerman et al., 2017; ESHRE 2018). For these reasons, Israel and Spain provide the right conditions to study the hypothesis of the geneticization of reproduction. At the same time, there are also significant institutional and cultural differences between both countries, which influence their ethical conceptions towards ART and their regulation, thus providing fertile ground for a comparative study.

Building on inputs from Delphi surveys and personal interviews and grounded on a previous technology forecast based on a panel of physicians from both countries (Alon et al., 2019), we discuss the potential trajectories for the diffusion of ART and present different scenarios. These scenarios may assist in building up some *anticipatory competence* that enables making strategic decisions and developing new frameworks to reshape the regulatory process in order to achieve the desired impacts

from technological innovations (Brown & Michael, 2003; Borup et al., 2006; Blind, 2008; Harmon, 2016).

To the best of our knowledge, this is the first attempt to use the Delphi method to question the viability of the geneticization thesis in reproductive care and to assess the challenges associated with expected developments in ART. This paper also contributes to broader studies on the diffusion of innovation, in particular to the strand of the literature that relies on qualitative methods to evaluate new technological developments by jointly considering supply, demand, regulation and the interactions between them (Nemet, 2009; Adner, 2015; Hammarberg et al., 2016). Therefore, it constitutes a novel empirical approach, which might inspire future studies dealing with the diffusion of medical technologies.

4.2. The geneticization of reproduction

Reproductive genetics includes various methods to control the outcome of reproduction prior to and during pregnancy. In this paper, we focus on the emergence of two forms of reproductive genetics, PGD and GE, which hold great potential for human enhancement and are also the source of heated social controversies.

The geneticization of reproduction could be the result of a significant increase in the scope of disorders subject to correction through reproductive genetics. It involves a shift in the focus of genetic testing, from diagnosing monogenic disorders of early onset and high level of penetrance (such as cystic fibrosis, sickle cell anemia, and fragile X syndrome), towards addressing less severe disorders of later onset and partial penetrance level (such as most metabolic, cardiovascular, cancerous and neurological diseases) (Klitzman, 2008; Batzer & Ravitsky, 2009). Today, PGD is already used for some polygenic diseases of late onset and partial penetrance, such as neurodegenerative disorders and hereditary cancer (Altarescu et al., 2015; Dagan et al., 2017). Further diffusion of reproductive genetics technologies would largely depend on their capacity to deliver enhanced children whose health is easier (and cheaper) to maintain (Greely, 2016; Knoepfler 2016).

Expectations, imaginaries and fears occupy a pivotal role in the innovation process by shaping its potential (Brown & Michael, 2003; Borup et al., 2006). Several authors have expressed high expectations regarding reproductive genetics in terms of human enhancement (Savulescu, 2001; Harris, 2007; Murphy, 2014). Conversely, intense preoccupations have also been expressed concerning these technologies; particularly regarding undesirable collateral effects leading to epigenetic implications and future health consequences to those who descent from ART and their future generations (ESHRE, 2014; Fauser et al., 2014; Nuffield Council on Bioethics, 2018).

Moreover, many authors have argued that the geneticization of reproduction would reduce human diversity and might lead to modern eugenics, i.e., the desire to enhance society with stronger, smarter and "better" people (Lippman, Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities, 1991; Garland-Thomson, Human Biodiversity Conservation: A Consensual Ethical Principle, 2015). Others have raised concerns over increasing social inequalities, expressed by discrimination in job opportunities and insurance coverage, due to unequal access to reproductive genetics (Buchanan et al., 2000; Fukuyama, 2002; Sandel, 2004; Wailoo & Pemberton, 2006). Furthermore, Silver (1997) has suggested that, in a distant future, such a "geneticization arms race" could lead to polarization of society. Privileged societal groups, be it the wealthier people or some elites within them, would evolve so far through genetic enhancement that at a certain point the "gen-rich" groups would completely lose interest in mixing or sharing anything with the "regular" people, and even crossbreeding between races would become unfeasible.

From a more philosophical stance, the ambition to design children has been criticized as weakening instead of empowering, since by imposing our desires and beliefs on future generations, we would undermine their autonomy and deny their right for an open future (Ramsey, 1972; Jonas, 1984; Fukuyama, 2002; Habermas, 2003; Sandel, 2004). As anticipated by Lewis (1947, p. 37-39): "The final stage is come when Man by eugenics, by pre-natal conditioning (…) has obtained full control over himself. Human nature will be the last part of nature to surrender to Man. The battle will indeed be won. But who, precisely, will have won it?"

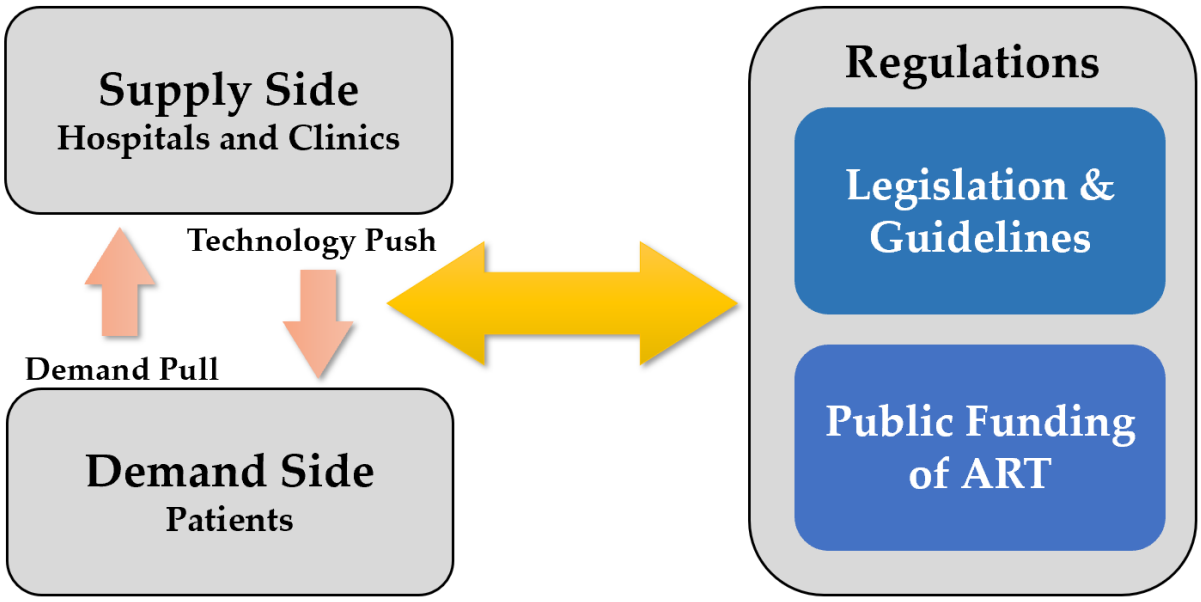
Nevertheless, at least three conditions must be met for further diffusion of reproductive genetics which might materialize these extreme scenarios. First, technological developments should make IVF safer, more comfortable and efficient. Second, reproductive genetics must introduce real or perceived medical or non-medical benefits in order to persuade the public to substitute natural reproduction with ART. Third, regulations should be set in alignment with these developments and allow a broader portfolio of reproductive genetics.

Diffusion of innovation is a multi-cycle, two-way process of communication between different agents in society (Rogers, 1983), and often described as an interaction between supply and demand. The technology-push approach states that advances in scientific understanding determine the rate and trajectories of innovation, while the demand-pull perspective identifies market features and changes in customers' needs as the factors directing innovation toward the desired outcome (Walsh, 1983; Nemet, 2009; Di Stefano et al., 2012).

To approach the geneticization of human reproduction at the confluence of technology-push and demand-pull forces, we also rely upon the following two theoretical constructs. Firstly, the "spiral-

shaped" process described by Beck-Gernsheim (2000) is relevant from a regulatory perspective, since it defines technology as an effect and a cause simultaneously and stresses the influence of technology over values and needs. The relationship between regulation and innovation is neither static nor single-directional but rather reciprocal, since regulation affects innovation and, in turn, the outcomes of an innovation create new conditions to be regulated (Paraskevopoulou, 2012) and also alter the social values upon which regulation is based upon (Beck-Gernsheim, 2000). Secondly, the "dual process" theory is useful for our purposes insofar as it distinguishes between two cognitive routes in decision-making: a "systematic processing" that relates to the conscious and observable improvement in outcomes (i.e. healthier babies) and a "heuristic processing", which relates to the unconscious (i.e. the formation of social imaginaries created by desires and expectations) (Rommetveit, 2011; Jiahua et al., 2016; Tarkkala et al., 2018).

Figure 1 – Interactions of supply, demand and regulations in ART.



Source: own elaboration

In the rest of this section we develop an analytical framework for analyzing the diffusion of ART from the supply, demand and regulatory perspectives, as sketched in Figure 1. Regarding each of these three components, we rely on a forecast elaborated in our previous work (Alon et al., 2019), which will later assist us to develop scenarios concerning the diffusion of ART and the geneticization thesis.

4.2.1. Technical factors

In four decades, IVF has improved substantially, offering solutions to infertile couples, single women, same-sex couples, carriers of genetic disorders and patients with a need or desire to preserve

their gametes by cryopreservation. For more far-reaching medicalization of human reproduction, IVF combined with reproductive genetics may enable to produce “healthier” children than natural reproduction. Nevertheless, there are some technical requirements and social limitations for such development to materialize.

IVF cycles begin with controlled ovarian hyperstimulation, a process which bears several health risks and inconveniences (Aragona et al., 2011; La Marca & Sunkara, 2014). It enables the ovaries to produce several eggs (with significant disparities between patient and cycles), which are then extracted (Cai et al., 2011). Subsequently, the retrieved eggs are placed in semen for fertilization to take place. Alternatively, fertilization can be conducted by injecting one spermatozoon, selected according to its morphology, directly into the cytoplasm of each egg by intracytoplasmic sperm injection (ICSI), which is currently used for the majority of IVF cycles in the U.S. and Europe (Palermo et al., 2009; CDC, 2018; ESHRE, 2018). As a result, few eggs are fertilized and become embryos available to be transferred to the uterus. According to different national registries, nowadays IVF is producing, on average, around 30% birth rates per cycle with non-donor eggs for women younger than 35 years, although success rates are decreasing in more advanced age groups (SEF, 2016; CDC, 2018). According to experts, we may expect a significant growth in these rates up to 50% within 20 years, due to improvements in methods of embryo selection, incubation, laboratory conditions and quality control (Alon et al., 2019).

The addition of PGD requires extracting DNA from a biopsy taken from each embryo prior to implantation, which is then diagnosed for pre-identified mutations (Milachich, 2014). Currently, PGD requires an extensive pre-study of family members to identify a single mutation associated with a severe disorder (Altarescu et al., 2015). Thus, PGD is a labor-intensive procedure (Wang, 2014) and must be customized for each couple (Swanson et al., 2007). In recent years, next-generation sequencing has been introduced, potentially allowing to infer the full genome sequence of every embryo in a more efficient manner (Nuffield Council on Bioethics, 2018).

Biopsies can also be used for preimplantation genetic screening (PGS), a global quantitative analysis of the entire genome which serves to detect and transfer only euploid embryos. This procedure assumes that an euploid embryo (i.e., without chromosomal structure anomalies) has better chances to develop into a fetus and be born as a healthy baby (Lu et al., 2016; Casper et al., 2017). PGD cycles represent a minor share of all IVF cycles. In fact, PGS is more commonly used and is mainly offered to patients of advanced age whose eggs tend to have higher levels of aneuploidy.

Next-generation sequencing also enables the whole exome sequencing. The exome makes up only 1.5% of the whole genome, but it contains all protein-coding genes. It has been estimated that more

than 10,000 monogenic disorders affect around one percent of humans at birth, and about two percent of couples carry a single gene variation that could result in a child with a severe genetic disorder (Aslamkhan, 2015; Babar, 2017; Nuffield Council on Bioethics, 2018). However, the detection pace of new monogenic disorders is declining while, in contrast, detection pace of polygenic disorders and multifactorial traits, which affect a much larger share of the population, is increasing (Nuffield Council on Bioethics, 2018; Second International Summit on Human Genome Editing, 2018a). This means that, with further developments in genomics, we can expect a higher utility of PGD, although according to experts, it will primarily be related to elderly diseases which are mainly multifactorial (Alon et al., 2019).

Performing an "expanded PGD" (i.e., diagnosis of various complex polygenic or multifactorial disorders, or whole exome PGD) would require a dramatic increase in the number of fertilized eggs, which would enable to detect a "perfect" embryo. Some experts suggest that such an abundant supply of eggs could be attained by stem-cells derived gametes (Shulman & Bostrom, 2014; Greely, The End of Sex and the Future of Human Reproduction, 2016), but this is yet a distant and unclear technological enhancement. Overall, expert geneticists and gynecologists have forecasted that it is hard to expect significant technological advances in eggs retrieval in the next two decades (Alon et al., 2019).

Alternatively, advances in GE, and mainly the introduction of CRISPR/Cas, may enable a much broader manipulation of human genetic traits. Developed in 2012, CRISPR/Cas is a simple, low-cost tool for gene editing, using the enzyme Cas9 as a pair of molecular scissors, which enables to cut strands of DNA. Its advantage over PGD could be that only a few embryos would be required, and for each embryo, various DNA fragments could be edited. In addition, traits of a third source could be added, meaning that the embryo would not be limited to the genetic material of the parents.

Nonetheless, CRISPR/Cas is still an emerging technology, which shows both great promise and considerable uncertainty. Germline modification carries significant risks since the introduction of alleles may create unintended side effects which would only be recognized in future generations. Also, once such a destructive gene edit is introduced there is currently no method to remove it (Evitt et al., 2015; Nuffield Council on Bioethics, 2018). Although it is not regularly practiced, in November 2018 it was announced that, despite the lack of consent by the scientific community, clinical gene-editing of embryos had been conducted in China, leading to the birth of the first two CRISPR/Cas edited babies (Krimsky, 2019).

Lastly, despite the expected technological improvements in IVF, implanting an embryo in the uterus is not a guarantee for success. Therefore, following the use of PGD or CRISPR/Cas, transferring the selected or designed embryo into the uterus will provide no promises of a live birth.

4.2.2. Demand for ART

According to different estimations, infertility affects 10-15% of the human population (Spar, 2006; Agarwal et al., 2015; ASRM, 2015). Moreover, the use of ART for social reasons has gained public consent in many countries, expanding the demand from women beyond the age of fertility (by egg donation), single women and same-sex couples. In addition, cryopreservation of gametes has created a new channel of demand, with elective fertility preservation gaining popularity.

As a result, IVF births already approximate or exceed 5% of the total in several countries (SEF, 2016; ESHRE, 2018; Ishihara, 2019; Health Ministry of Israel, 2018), and embryo selection by PGD/PGS has gained popularity, accounting for 22% of IVF cycles in the U.S. in 2016.

Some evidence shows that, in recent years, infertility has been rising due to environmental hazards and unhealthy lifestyles (Boivin et al., 2007; Mascarenhas et al., 2012; Inhorn & Patrizio, 2015; Sobotka, 2016). Additionally, age-related infertility has been a central factor due to the rise in the average age of parenthood. It has even been suggested that excessive trust in ART may create false anticipations, leading individuals to expect childbearing at an advanced age and postpone parenthood as a result (Hashiloni-Dolev et al., 2011; Machado & Galdeano, 2011; Chan et al., 2015; García et al., 2017; Fauser et al., 2019). Nonetheless, most people are fertile, tend to reproduce early enough, carry no significant genetic disorders, and settle for prenatal genetic testing to avoid birth of children with severe disorders. Would demand then face a glass ceiling?

For further diffusion, ART must address new channels of demand. On top of the facilitation of treatment, improvements in reproductive genetics must bring along promises of significant benefits to the public to overcome the physical, emotional, and financial burden of the medical procedure. Proven health benefits concerning less severe polygenetic disorders and diseases (which appear at a lesser level of penetrance, with later onset, and affect a much larger share of human population), would constitute the *conscious* aspect of this dual process. However, such benefits could take a long time to be demonstrated, if at all. Therefore, at the *unconscious* facet of the dual-process stands the creation of socio-technical imaginaries induced by market forces, which may breed desires, expectations and new perceptions of health benefits that would in turn develop into needs and requirements, and later into parental and social responsibilities (Rommetveit, 2011; Tarkkala et al., 2018).

In this respect, previous predictions for demand (Alon et al, 2019) suggest that within 20 years the percentage of IVF births could reach more than 14% in Israel and Spain, mainly due to age-related infertility. Moreover, approximately 40% of IVF cycles could involve PGD, meaning that, while it might

not be the primary factor inducing the demand for IVF, PGD would become a very common add-on to treatments.

4.2.3. Regulation

Embryo selection by PGD began as a very controversial technology, raising ethical concerns regarding the deliberate waste of human embryos, the suggestion that physicians are "playing god", and the possibility of reaching a "slippery-slope" where practicing genetic selection for a growing number of disorders could eventually lead to eugenics (Zuckerman et al., 2017). Nevertheless, PGD has been progressively gaining consent since its introduction almost 30 years ago, as it allows parents carrying genetic disorders to bring a healthy child into the world, while many seek such solution following the birth of a child affected with a severe genetic disorder. After all, PGD saves a great deal of emotional and financial resources associated with caring for a child with a "life not worth living", i.e. with very short life expectancy, intense medical care demands, and very poor quality of life (Buchanan et al., 2000).

In most countries, PGD is still highly regulated and practiced in accordance with the characteristics of the genetic conditions under diagnosis. These are defined by the severity of the disorder, by being monogenic or polygenic, of early or late onset, of a high or low level of penetrance, and by being curable or non-curable. Originally, PGD was used mainly for severe, non-curable monogenic disorders of full penetrance and early onset. However, regulation of reproduction genetics evolves following a *spiral-shaped process*, whereby values and needs boost the development of technology and its cultural acceptance, while simultaneously the very existence of the technology redefines values and needs (Beck-Gernsheim 2000).

At first, the use of PGD to avoid the birth of a child with an extremely short life expectancy was rather easily justified. Later, its success increased the level of public consent also in less extreme scenarios, and the availability of the technology has produced higher acceptance to use it for a growing set of severe disorders, some of later onset and incomplete penetrance. In a previous study, although most experts supported many sorts of PGD, they drew a clear red line between medical and non-medical uses of the procedure, showing a strong opposition against applications of reproductive genetics to identify and select physical characteristics or cognitive traits (Alon et al., 2019). Nevertheless, PGS is also gaining medical justification and social consent, thus becoming more frequently practiced in order to increase IVF success rates (Klitzman, 2009; Batzer & Ravitsky, 2009; Pavone & Arias, 2012).

Moreover, at the next step of reproductive genetics, CRISPR/Cas could provide a more efficient and effective solution. Trials on human embryos have been elaborated with growing success rates, but

there is a “tacitly agreed” temporary moratorium on implanting genetically edited embryos into the uterus (Evitt et al., 2015). This consensus, however, was recently broken unexpectedly by one researcher in China, with uncertain consequences (Krimsky, 2019). Following this event, discussions at the 2nd International Summit on Human Genome Editing of 2018, concluded that three conditions are required to approve the use of CRISPR/Cas on human embryos: (1) scientific rationale (medical justification), (2) safety and (3) social acceptance (Second International Summit on Human Genome Editing, 2018b), which currently are not fullfiled. Further proof for safety and efficiency considering risks of multigenerational side effects, as well as more ethical debate leading towards a better regulatory framework, must occur before CRISPR/Cas becomes an acceptable therapeutic tool.

4.3. Methods

To further assess the geneticization thesis and its regulatory implications, we conducted a Delphi consultation with a panel of experts from different fields related to ART, to simulate two typical advisory committees (from Israel and Spain).

We began by conducting semi-structured personal interviews with 29 experts. We approached these interviews considering our insights from a previous forecast (Alon et al., 2019) in an attempt to confront these Israeli and Spanish experts with the conclusions drawn by physicians in those countries. The core purpose of these interviews was to assist in building a Delphi questionnaire, although they also served to provide broader qualitative insights and to detect more participants based on recommendations by the interviewees, propitiating a “snowball” effect (Ribeiro & Quintanilla, 2015).

The participants were selected based on their skills, experience and unique contribution to public discourse (Lock, Towards a National Bioethics Committee, 1990). For this purpose, we consulted members’ lists of the Spanish bioethics committee, and the latest (2012) government appointed Israeli “Mor-Yosef” committee (since in Israel advisory committees are occasionally appointed). The panel included 18 Israelis and 18 Spaniards, 21 women and 15 men. We selected experts of a multidisciplinary character as common in bioethics committees (see Bagheri et al., 2016; Gomes de Oliveira et al., 2017). All experts had interest in the ethical debate and their careers were dedicated to ART from the fields of medicine (12), law and bioethics (7), public health (5), psychology (3), biology (2), philosophy (2), economics (2), epidemiology (1), theology (1) and journalism (1).

The questionnaire dealt with general attitudes towards regulations, and with specific practices of reproductive genetics. It was based on 10-point scale questions and was complemented with open spaces for comments. Due to the experts’ low availability, the Delphi survey was limited to two rounds

regardless of the degree of consensus achieved, a methodologically sound practice (Landeta, 2002; Von der Gracht, 2012; Dayé, 2018).

Between the rounds, we highlighted for each expert those answers which significantly differed from the central tendencies and asked regarding inconsistencies or substantial deviation from the group, using a controlled feedback (Landeta et al., 2008; Skirton et al., 2013). The participants were offered the option to change their replies or add explanatory comments regarding their deviant positions. This method provides either consensus regarding regulatory approach or qualitative insights to explain dissensus which may assist to construct alternative scenarios (Okoli & Pawlowski, 2004; Landeta & Barrutia, 2011; Melander, 2018).

Our statistical analysis is mainly based on descriptive statistics focusing on central tendency (mean) while the level of consensus was measured by the standard deviation (SD) (Von der Gracht, 2012). The statistical analysis was complemented with qualitative insights gathered through personal interviews and open comments from the questionnaire, which were essential to interpret the results and explain experts' consensus and dissensus.

4.4. Results

The two panels, simulating bioethics committees from Israel and Spain, were asked for their attitudes towards the regulation of reproductive genetics and their approaches to the regulation of different medical applications. We aimed to identify the red line of reproductive genetics and the factors that motivate the regulator to ban certain applications of these technologies.

4.4.1. General attitudes towards regulations

Focusing on the spiral-shaped process of reproductive genetics, we introduced four different statements and asked the panels to mark their level of support (from 1 -completely opposing- to 10 -completely supporting-). The answers are shown in Table 1.

Table 1. General attitudes towards the regulation of PGD

From 1 (completely opposing) to 10 (completely supporting)	Israel (18)		Spain (18)	
	Mean	SD	Mean	SD
a. The public sector should aim at reducing regulation regarding PGD to a minimum in order to allow the patients maximum free choice.	3.4	2.83	3.7	2.79
b. When performing PGD for medical reasons, sex selection as an add-on service should be allowed. In-other-words, the physician may reveal the sex of the (clinically) selected embryos enabling the patients to choose sex if it does not interrupt with the treatment.	2.8	2.76	2.2	1.63
c. When performing IVF due to infertility, regulation should be more tolerant towards PGD. It should be allowed as an add-on service to IVF for some range of disorders.	7.9	2.51	6.3	2.66
d. It is viable in terms of regulation to separate between the use of PGS and the use of PGD for detecting disorders. In other words, in case PGS will eventually become a very common add-on for IVF cycles to increase the prospects of the treatment, regulation may still prevent the clinics from regularly using the biopsies taken for PGS to perform PGD.	4.8	2.25	5.6	2.37

Replies to statement a. show that the experts did not support the liberalization of reproductive genetics. From a medical perspective, most experts supported the promotion of PGD to minimize future genetic diseases. Additionally, the panels supported regulation to reduce unexpected risks. As stated by one of the interviewees: *"In the long run, we may find that by trying to prevent cancer by PGD, we increased the incidence of other cancers or malformations (exposing the fertilized egg to radiation, light, laboratory temperature, materials and more). Not enough years have passed, and not enough treatments were done to make us confident in the safety of these techniques."*

Some experts also marked the importance of reducing asymmetric information, emphasizing that the technology is very sophisticated, and people are not usually familiar with all its implications. According to one expert: "*Regulation should ensure safe and evidence-based services, make sure the offer of PGD is accompanied by appropriate counseling, and that the important decision to perform IVF for the sake of PGD is fully informed and free of pressure*". Moreover, it was claimed by another that "*we should prevent society from falling into the false belief that reproductive genetics assures 100% healthy offspring (…) we should not fall into genetic determinism when many other factors can influence people's health and quality of life. Taking the use of PGD to the extreme in order to rule out any minimum possibility or genetic risk is to favor a false reality, nothing reasonable or prudent".*

Further ethical claims supported limiting PGD to avoid eugenics, and due to the slippery-slope argument. *"The process of selecting 'perfect' embryos occurs gradually, and we become accustomed to the idea so that later it will seem natural to prevent the birth of infants with treatable diseases or even traits that we have no reason to prevent"*.

Although most experts supported regulating the field, some advocated the consideration of personal autonomy as much as possible, urging to *"avoid heavy-handed regulation of PGD and leave the reproductive decision making to women and couples, based on a principle of reproductive autonomy"*. However, it was also stated that *"patients' choice and their consent for therapies should take place within a normative framework and a public health system. Therefore, the freedom of choice cannot be total".*

As we may further learn from statement b., the panel opposed revealing gender upon performing PGD. Comments emphasized the fear that allowing it would turn every PGD into a sex-selection. In contrast, according to statement c., PGD as an add-on to IVF was approved by the panels (more strongly by the Israeli), which underlined again the priority given to preventing medical disorders.

It is also interesting to note that several experts raised the slippery-slope argument in their open comments: *"The definition of 'a range of disorders' is very vague… The question is where it will lead and where the boundaries are"*; *"Why for a variety of genetic diseases rather than genetic anticipation or next-generation sequencing? Why (IVF) only for infertility and not for couples who want to avoid pregnancy breaks?"*

Finally, concerning statement d., the experts were doubtful regarding the ability to stretch a line between PGD and PGS in case the latter becomes a standard add-on to IVF. In the words of one of the experts: *"There is a regulatory weakness in this regard because the line is very loose. Where settings are not sharp, regulation will lose..."*. This problem was occasionally raised by other experts too, who found difficulties to identify a possible solution.

4.4.2. Regulation of specific practices of reproductive genetics

Following the analysis of general attitudes towards PGD reported in the previous section, Table 2 presents experts' attitudes towards specific applications of reproductive genetics. We distinguish three different levels of consent: strong support, mild support and disapproval, each marked with different colors in the table.

Table 2. Specific attitudes to reproductive genetics

From 1 (completely opposing) to 10 (completely supporting).		Israel (18)		Spain (18)	
		Mean	SD	Mean	SD
a. PGD for severe monogenic disorders of **early-onset** and high-level of penetrance with no simple cure.	Allow	9.6	0.62	9.3	2.20
	Fund	9.5	0.64	8.9	2.30
b. PGD for severe monogenic disorders of **medium-late onset** and a high level of penetrance with no simple cure.	Allow	9.4	0.81	8.9	2.19
	Fund	9.2	0.94	8.5	2.35
c. PGD for severe monogenic disorders of **medium-late onset** and a **medium level of penetrance** with no simple cure.	Allow	7.5	2.22	8.6	2.43
	Fund	6.9	2.29	8.1	2.60
d. GE (CRISPR/Cas) for severe monogenic disorders of early-onset and high-level of penetrance with no simple cure in case PGD did not provide a solution.	Allow	7.5	2.29	6.4	3.39
	Fund	6.5	2.79	4.8	3.51
e. PGS for detection of **chromosomal abnormalities**, in order to increase the prospects of an IVF treatment.	Allow	6.9	2.79	6.2	3.29
	Fund	5.7	2.97	4.3	3.24
f. PGD for **multifactorial diseases**, (cancerous/ metabolic/ cardiovascular/ neurological) with **medium-late onset** and **medium level of penetrance**.	Allow	6.4	2.60	6.0	3.28
	Fund	5.2	2.34	4.3	2.66
g. PGD with **whole exome screening**.	Allow	3.8	2.29	4.3	3.15
	Fund	2.6	2.22	3.1	2.82
h. PGD for **social sex selection**.	Allow	2.1	1.88	3.7	3.37
	Fund	1.8	1.51	1.4	1.42
i. PGD for **cognitive characteristics** selection.	Allow	1.3	1.19	1.5	1.29
	Fund	1.4	1.22	1.3	0.96
j. PGD for **physical traits** selection.	Allow	1.3	1.19	1.3	0.97
	Fund	1.4	1.22	1.3	0.96

Strong support (green zone)

The experts strongly supported, with a high level of consensus, the use of PGD for monogenic disorders of a high level of penetrance either with early or late onset. However, there was a lower consensus regarding the use of PGD for disorders of medium level of penetrance (including many cancerous diseases), with the Spanish panel expressing stronger support compared with the Israeli. Despite the lack of consensus, both the Spaniards and the Israelis tended to allow and fund such PGD, as stated by one interviewee: *"We are not talking here about curable diseases. Some genetic disorders*

of 'medium level of penetrance' are in practice devastating cancers which may affect various members of a family".

The experts mostly supported the coverage of PGD by the public system in order to, as explained by their comments, avoid health inequalities and guarantee that families with a medical history of hereditary diseases could have fair access to the technology.

Mild support (grey zone)

The panel displayed less consensus regarding four contested categories of which health benefits are not yet clear:

- Concerning CRISPR/Cas for germline editing, we presented the panel with a specific case referring to a severe disorder of early onset and high level of penetrance in which PGD cannot be delivered since there were very few eggs/embryos. The panel expressed reasonable support in this case, and the main preoccupations were about safety, beneficence principle, efficiency and low cost. The slippery-slope argument was not raised in this context.
- With respect to PGS for chromosomal abnormalities, some comments emphasized the undemonstrated usefulness or cost-effectiveness of the technique. One expert stated that *"PGS is contraindicated in the following cases: advanced maternal age, early ovarian failure, low response, poor embryo quality, severe male factor and more".* Various experts expressed preoccupation regarding the increased use of PGS, claiming that it is occasionally offered as an add-on to IVF cycles, increasing financial burden on patients (as it is not publicly funded) only to produce significant gains to private clinics.
- Regarding PGD for Multifactorial diseases, the experts distinguished between diseases *"for which there is a genetic cause with a reliable diagnosis and for which PGD should be allowed and financed"*, and other multifactorial diseases which cannot yet be diagnosed by PGD and therefore *"should be strictly regulated and not financed"*. One expert claimed that *"there are no immediate perspectives that* PGD *contributes anything significant regarding disorders involving more than a single gene or when a larger number of factors cause a disease".*
- The experts did not express high support for using PGD for whole exome screening. As explained by one expert: *"I reject the use of techniques that are not directly preventing or treating diseases, for which safety is not guaranteed or whose impact and consequences on the human species are yet unknown"*. An important point raised was: *"The problem is that there will always be some suspicious mutations (although emphasis will be given only to areas where there is a family history or where a gene for carriers has been identified), but if each finding were revealed to the patient, there would be no embryo remained to implant".*

For all questions differences between "allowing" and "funding" the procedures were noticed. Some experts explained these differences along the following lines: *"The public system, always with limited resources, should prioritize the financing of other health needs, rather than PGD for multifactorial diseases, which could lead to an uncontrollable demand"*; "*It is essential from an ethical perspective to distinguish what would be allowed from what would be financed. Allowing these procedures would enable autonomy for couples in decisions concerning their children's health. Another issue is financing these procedures with public funds when we have many other urgent priorities regarding health issues that are not subjected to probability."*

Disapproval (red zone)

Finally, PGD for non-medical needs was discarded by the experts as inadvisable. As stated by one expert: *"The ethical boundary regarding the application of PGD should be between avoiding hazards and satisfying preference or choice of characters, simply according to the parent's preference and not for the future benefit of an individual. I can accept the application of scientific knowledge to avoid suffering but not to satisfy whims".* Furthermore, the idea to fund these procedures was rejected almost unanimously.

Nevertheless, a few comments from the panel were tolerant towards sex selection: *"it should be considered in some cases (couples with few children of the same gender who are psychologically affected by the lack of offspring of the other gender). There would be particular cases, and it is not necessary to criminalize them";* and particularly regarding Israel: *"Sex selection in this area of the world is sometimes much more than merely 'social' and understandably allowed if having the 'wrong' sex baby might jeopardize either the mother or the baby".*

4.5. Discussion

Despite the different cultural and institutional background of both countries, an insightful result of our study is the similarity between the answers of experts from Spain and Israel across most dimensions. The central message raised by both panels was that almost any use of ART which is safe enough and provides significant health benefits should be approved. The experts awarded health interests and individual autonomy the highest importance, although they remained cautious and attentive to some potential social risks.

The attitudes expressed by the two panels simulating "bioethics committees" only slightly differed from those expressed by a panel of physicians from Israel and Spain in our previous study (Alon et al., 2019). The "bioethics committees" were more conservative towards the use of multifactorial diseases

of medium-late onset but more permissive concerning the use of CRISPR/Cas (i.e., the physicians seem to be more aware of the unexpected risks derived from this new technology). Moreover, both the "committees" and the "physicians" strongly rejected non-medical applications of reproductive genetics (Alon et al., 2019).

Based on the main results of the Delphi panels described in Section 4, supplemented by our previous forecast (Alon et al., 2019), we can now proceed to evaluate the extent of geneticization of human reproduction by dividing it into two stages and presenting two possible scenarios at the second stage.

Stage 1. Reproductive genetics as an add-on to IVF: This stage of geneticization is, to a great extent, already being realized today in Israel and Spain. In the following decades, improvements in IVF will resolve more pathologies of infertility. The demand for IVF will increase primarily due to the postponement of parenthood, the rise of age-related infertility and fertility preservation. Additionally, environmental factors, unhealthy lifestyles, the use of PGD and social uses of IVF will shift demand upwards (Alon et al., 2019). Meanwhile, PGS will become a more standard add-on, and biopsies will increasingly be used for PGD, which will enable detecting a more extensive variety of disorders, multifactorial, of later-onset, lower level of penetrance and even less severe expressions, using non-invasive methods and providing higher accuracy and success rates (Lu et al., 2016).

According to the panels, regulation in Spain and Israel should keep approving medical practices of ART that promise health benefits, and preferably guarantee public coverage to assure fair and equal distribution, considering that resources are limited. The experts were not sure regarding regulators' ability to separate PGS from PGD. More importantly, applying PGD as an add-on is reasonably accepted by the panels, providing that there are apparent medical reasons.

Later at this stage of diffusion clinical GE of human embryos will be introduced, beginning with some cases where PGD fails to deliver.[3] Both panels were positive regarding the future application of CRISPR/Cas in embryos for therapeutic means, following a further societal debate and a growing international consensus (see also Second International Summit on Human Genome Editing, 2018b). Unless inappropriate use with disastrous results generates public mistrust in this technology, CRISPR/Cas will eventually be perceived as more practical, efficient (requires fewer embryos) and more potent than PGD. Nonetheless, it is likely to be a long and gradual process, and even after the

[3] The possible uses would be: Y-chromosome defects; inversions and deletions of chromosome segments; dominant genetic conditions such as Huntington's disease, some forms of Alzheimer's disease or breast cancer, where one of the prospective parents is homozygous; recessive genetic conditions where both parents are homozygous (Nuffield Council on Bioethics, 2018).

first applications of CRISPR/Cas, preoccupations with safety and adverse effects will take time to dissolve.

Potentially, with CRISPR/Cas breaking through, a much wider variety of possibilities could be opened, from replacing whole genes to fixing aneuploid embryos, and even aiming at cure complex multifactorial diseases. CRISPR/Cas might be revolutionary or age defining, but it is yet early to measure the relative impact of genetic factors on the many characteristics that people may wish to influence. It is therefore hard to foresee the potential uses of genome editing, and it might also be limited for an extended period to single gene disorders and a few more conditions of limited complexity (see also Nuffield Council on Bioethics, 2018).

At the end of this stage, around 15% of births in these countries will be due to IVF. Moreover, about 40% of the cycles would include reproductive genetics, and gradually more benefits of PGD and GE will be recognized. However, the use of reproductive genetics will still concern a limited share of the population (those with a medical history of hereditary diseases).

Stage 2 – Reproductive genetics for the mass: After maximizing the IVF potential as a solution to infertility, the only channel for the market to grow further would be reproductive genetics, i.e., IVF dedicated for PGD or GE. However, in recent years many concerns were raised that the use of IVF and PGD increases risks for congenital damage, cancerous and cardiovascular diseases, developmental deficiencies and cognitive disorders (Fauser et al., 2014; ESHRE, 2014). Also, similar worries regarding CRISPR are already being raised (Evitt et al., 2015). Further evidence, proofing or refuting these concerns, will have significant weight on the second stage of diffusion since referring fertile couples with “good genes” to reproductive genetics will most likely be discarded in case that high risks are being perceived.

We may now speculate about two divergent scenarios:

a) *A market for desires***:** New findings in genomics may enable expanded PGD and CRISPR for multifactorial diseases and traits, although most children are healthy, and most people do not suffer severe health conditions during their early and mature lives. For the average person, the greatest advantage of extended PGD would be related to elderly diseases (Alon et al., 2019). Therefore, driving the public to approach reproductive genetics could be done mostly by promising to deliver children who will be more resistant to such diseases, or by enabling the selection of physical and cognitive traits.

Nonetheless, the panels strictly rejected the use of reproductive genetics for non-medical reasons, and it may take decades until these moral views might shift toward acceptance. Also, from a medical

perspective, it may take a lifetime to prove benefits from an expanded PGD which aims at diseases of very late onset. Obtaining such proofs will depend on conducting follow-up throughout the adult lives of ART babies, a task for which scientists are already struggling with today. In their absence, evidence could be replaced by scientific speculations, beliefs and expectations, with socio-technical imaginaries generating perceived benefits of geneticization.

Once physicians and patients are encouraged by supportive scientific publications, and regulators are aligned, the second stage will be underway. The competition between "embryo designers" will thrive, and the promise of a 'perfect baby' will nourish the deepest desires of parents. Reproductive genetics will ultimately turn into parental responsibility and end up as a social norm.

b) *A limited market*: Alternatively, despite the many technological developments, the remarkable improvements in IVF outcome and the benefits of reproductive genetics, more than 80% of the people do not require ART. They are fertile, opt to give birth early enough, and find no specific motivations to seek a genetically selected or engineered baby. After all, we can expect improvements not only in reproductive medicine but also in other fields. Why should people approach ART despite the physical and financial burden, only to design a baby resistant to complex diseases which could be cured or even prevented in a more efficient way?

As explained previously, the share of the human population affected by monogenetic or relatively simple polygenetic disorders is quite limited (Aslamkhan, 2015; Babar, 2017). If reproductive genetics aims at moving towards multifactorial diseases and traits, it will encounter more cases of gene pleiotropy, i.e., when one gene controls the phenotype or expression of several unrelated traits (Nuffield Council on Bioethics, 2018). Such complexity could place severe limitations to reproductive genetics. Furthermore, with further knowledge of genomics, we may finally comprehend and accept the falseness of genetic determinism (Buchanan et al., 2000; Ravitsky, 2002; Birch, 2005).

Our work is not exempt from limitations. A Delphi panel selection always has a certain level of subjectivity: different experts may express distinct attitudes, particularly when many of the issues addressed here are subjected to value-based approaches. Moreover, our selection of countries which stand at an advanced stage of diffusion, have very pro-ART attitudes and tend to nourish a comprehensive public healthcare system, might have advantages but may also produce some biases. Different results might be obtained from countries where there is a strong attachment to individualism and free-market economic theories (such as the USA) (Johnson & Petersen, Public Interest or Public Meddling? Towards a Subjective Framework for the Regulation of Assisted Reproduction Technologies, 2008), or where the use of PGD is contested (i.e., Austria and Germany) (Hashiloni-Dolev

& Raz, 2010; (Griessler & Hager, Changing Direction: The Struggle of Regulating Assisted Reproductive Technology in Austria, 2017)).

Lastly, the reliability of forecasting is always limited due to the field's complexity. Many developments in genomics, prenatal testing and general medicine could change the "rules of the game" in ART, although it is not possible to include all these factors of potential technological developments in a single study. Nevertheless, many of the predictions introduced in this paper are compatible with recent literature (Lu et al., 2016; Casper et al., 2017; Nuffield Council on Bioethics, 2018).

4.6. Conclusion

The medicalization of reproduction is a long and observable process, beginning with the growing practice of IVF, which is currently being led mainly by infertility. In this stage, reproductive genetics may be further introduced as an add-on, based on a dual process in which, on the one hand, real outcomes are being produced and, on the other, imagined or uncertain outcomes are being perceived. After reaching a critical mass and producing more confidence in outcomes, the second stage may arrive where genetic selection and engineering could become the market's main growth engine.

The geneticization of reproduction will, therefore, not result from a "moment of breakthrough" (Brown & Michael, 2003) in a particular research project. Alternatively, it is a spiral shaped-process, influenced by gradual technology advances, socio-technical expectations and imaginaries, and shifts in public values. In this process, regulation interacts with supply and demand, having a key role in directing ART trajectories to the benefits of society, preventing adverse consequences and mitigatating the public's concerns and fears.

Our analysis in Israel and Spain unveils that the moral justification of using ART for infertility and prevention of genetic disorders stands firm. The experts attempted to draw a line between medical uses and non-medical uses of reproductive genetics, but there is a significant grey-zone between these two categories, which is likely to expand in the near future and complicate the regulator's task, as new technological developments materialize. At the first stage, the primary roles of regulation are to assure good practices and equity, correct information failures and verify the collection of data to enable a more accurate follow-up and research.

Concerning the possibility to step into the second stage of diffusion, and given the weight assigned by panelists to medical justification, if the benefits produced by reproductive genetics will be supported by evidence, the way towards further medicalization of reproduction will be paved.

Although such a scenario may still be far, the ART industry might gradually seek to expand by promising those unproven benefits, as in the case of PGS today (Orvieto & Gleicher, 2016; Casper et al., 2017). This brings us to conclude that despite the large economic benefits of the ART industry, regulators should aspire to slow down the medicalization process. This could be achieved by promoting the prevention of infertility and by better informing the public regarding infertility and ART outcomes (Chan et al., 2015; García et al., 2017; Fauser et al., 2019), including reproductive genetics. As ART is increasingly becoming a common way of reproduction, it is imperative for governments to enhance public awareness by disseminating clear information on its opportunities and risks.

Finally, as ART further develops, the importance of broad and inclusive international debate is growing. We may greatly doubt whether regulations in Israel, Spain or any other country are ready to welcome the stage of advanced reproductive genetics. In order to be better prepared it is important to conduct regulatory collaboration between countries, since state borders and national regulations will play a decreasing role at the second stage (see also Martin, 2014). We should avoid "sleepwalking" into this process by allowing uncontrolled technological momentum (Nuffield Council on Bioethics, 2018). However, we also should prevent basing our ideology on outdated and misleading contexts. In other words, preventing reproductive genetics for non-medical reasons is not a total guarantee for stopping geneticization and, similarly, allowing patients to take autonomous decisions (for instance, in the case of sex-selection) will not necessarily lead to social catastrophe. An open debate should address questions of freedom of choice and personal autonomy while being regularly updated according to the most realistic and accurate scientific context, to avoid falling into inflated hopes or dystopian theories.

References:

Adner, R. (2004). A Demand-Based Perspecitve on Technology Life Cycles. In A. M. Joel A.C. Baum, Business Strategy over the Industry Lifecycle (Advances in Strategic Management, 21) (pp. 25-43, doi: 10.1016/S0742-3322(04)21001-4). Emerald Group Publishing Limited.

Agarwal, A., Mulgund1, A., Hamada, A., & Chyatte, M. R. (2015). A Unique View on Male Infertility Around the Globe. Reproductive Biology and Endocrinology, doi 10.1186/s12958-015-0032-1.

Alon, I., Guimon, J., & Urbanos-Garrido, R. (2019). What to expect from assisted reproductive technologies? Experts' forecasts for the next two decades.

Aragona, C., Mohamed, A. M., Salomè B Espinola, M., Linari, A., Pecorini, F., Micara, G., & Sbracia, M. (2011). Clinical Complications after Transvaginal Oocyte Retrieval in 7,098 IVF Cycles. Fertility and Sterility, 95(1), 293-4. doi: 10.1016/j.fertnstert.2010.07.1054.

Aslamkhan, M. (2015). Clinical Genetics and Genetic Counselling in Pakistan. Journal of Genes & Cells, 1(2): p, 31-33, doi: 10.15562/gnc.17.

ASRM, P. C. (2015). Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility, 103(3), e18-25. doi: 10.1016/j.fertnstert.2014.12.103.

Babar, U. (2017). Monogenic Disorders: An Overview. International Journal of Advanced Research, 5(2) 1398-1424, doi: 10.21474/IJAR01/3294.

Bagheri, A., Moreno, J. D., & Semplici, S. (2016). Global Bioethics: The Impact of the UNESCO International Bioethics Committee. Springer International Publishing, doi: 10.1007/978-3-319-22650-7.

Batzer, F. R., & Ravitsky, V. (2009). Preimplantation Genetic Diagnosis: Ethical Considerations. In V. Ravitsky, A. Fiester, & A. L. Caplan, The Penn Center Guide to Bioethics. (pp. 339-354). New York: Springer.

Beck-Gernsheim, E. (2000). Health and Responosibility: From Social Change to Technological Change and Vice Versa. In B. Adam, U. Beck, & J. Van Loon, The Risk Society and Beyond: Critical Issues for Social Theory (pp. 122-134). London: Sage.

Bijker, W. E., Hughes, T. P., & Pinch, T. (1987). The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology. Cambridge, Mass: MIT Press.

Birch, K. (2005). Beneficence, Determinism and Justice: An Engagement with the Argument for the Genetic Selection of Intelligence. Bioethics, 19(1), 12-28.

Blind, K. (2008). Regulatory Foresight: Methodologies and Selected Applications. Technological Forecasting & Social Change, 75, 496–516, doi: 10.1016/j.techfore.2008.02.004.

Boivin, J., Bunting, L., A. Collins, J., & Nygren, K. G. (2007). International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. Human Reproduction, 22, 6. 1506–1512, doi: 10.1093/humrep/dem046.

Borup, M., Brown, N., Konrad, K., & Van Lente, H. (2006). The Sociology of Expectations in Science and Technology. Technology Analysis & Strategic Management, 18, 3/4, 285–298, doi: 10.1080=09537320600777002.

Brown, N., & Michael, M. (2003). A Sociology of Expectations: Retrospecting Prospects and Prospecting Retrospects. Technology Analysis & Strategic Management, 15:1, 3-18, doi: 10.1080/0953732032000046024.

Buchanan, A., Brock, D. W., Daniels, N., & Wikler, D. (2000). From Chance to Choice: Genetics and Justice. Cambridge University Press.

Cai, Q. F., Wan, F., Huang, R., & Zhang, H. W. (2011). Factors Predicting the Cumulative Outcome of IVF/ICSI Treatment: A Multivariable Analysis of 2450 Patients. Human Reproduction, 9, 2532-40. doi: 10.1093/humrep/der228.

Casper, R., Haas, J., Hsieh, T., Bassil, R., & Mehta, C. (2017). Recent Advances in in Vitro Fertilization. F1000Research, 6, 1616, doi: 10.12688/f1000research.11701.1.

CDC. (2018). Assisted Reproductive Technology - National Summary Report 2016. Atlanta, US, Centers for Disease Control and Prevention, American Society for Reproductive Medicine, https://www.cdc.gov/art/pdf/2016-report/ART-2016-National-Summary-Report.pdf.

Chan, C. H., Chan, T. H., Peterson, B. D., Lampic, C., & Tam, M. Y. (2015). Intentions and Attitudes Towards Parenthood and Fertility Awareness Among Chinese University Students in Hong Kong: A Comparison with Western Samples. Human Reproduction, 30, .2 364–372, doi: 10.1093/humrep/deu324.

Dagan, E., Birenbaum-Carmeli, D., Friedman, E., & Feldman, B. (2017). Performing and Declining PGD: Accounts of Jewish Israeli Women Who Carry a BRCA1/2 Mutation or Partners of Male Mutation Carriers. Journal of Genetic Counseling, 26, 5, doi: 10.1007/s10897-017-0087-6.

Dayé, C. (2018). How to Train Your Oracle: The Delphi Method and its Turbulent Youth in Operations Research and the Policy Sciences. Social Studies of Science, 48(6) 846–868, doi: 10.1177/0306312718798497.

Di Stefano, G., Gambardella, A., & Veronab, G. (2012). Technology Push and Demand-Pull Perspectives in Innovation Studies: Current Findings and Future Research Directions. Research Policy, 41(8), 1283-1295, doi: 10.1016/j.respol.2012.03.021.

ESHRE. (2018). Assisted Reproductive Technology in Europe, 2014: Results Generated from European Registers by ESHRE. Human Reproduction, 33(9):1586–1601. doi: org/10.1093/humrep/dey242.

ESHRE Capri Workshop Group. (2014). Birth Defects and Congenital Health Risks in Children Conceived Through Assisted Reproduction Technology (ART): A Meeting Report. Journal of Assisted Reproduction and Genetics, 8, 947-58, doi: 10.1007/s10815-014-0255-7.

Evitt, N. H., Mascharak, S., & Altman, R. B. (2015). Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework. The American Journal of Bioethics, 15(12): 25–29, doi: 10.1080/15265161.2015.1104160.

Fauser, B. C., P., D., Diedrich, K., B. B., Bonduelle, M., Delemarre-van de Waal, H. A., . . . Wells, D. (2014). Health Outcomes of Children Born After IVF/ICSI: A Review of Current Expert Opinion and Literature. Reproductive BioMedicine Online, 2, 162-82, doi: 10.1016/j.rbmo.2013.10.013.

Fukuyama, F. (2002). Our Posthuman Future, Consequences of the Biotechnology Revolution. New York: Farrar, Straus and Giroux.

García, D., Vassena, R., Prat, A., & Vernaeve, V. (2017). Poor Knowledge of Age-Related Fertility Decline and Assisted Reproduction Among Healthcare Professionals. Reproductive Biomedicine Online, 34, 1, 32-37, doi: org/10.1016/j.rbmo.2016.09.013.

Garland-Thomson, R. (2015). Human Biodiversity Conservation: A Consensual Ethical Principle. The American Journal of Bioethics, 15(6):13-5. doi: 10.1080/15265161.2015.1028663.

Gomes de Oliveira, M. C., A. d., & Nogueira-Martins, M. C. (2017). The Experience of the Bioethics Committee from a Public Hospital. Revista Bioetica, 25 (2): 338-47, doi: org/10.1590/1983-80422017252194.

Greely, H. T. (2016). The End of Sex and the Future of Human Reproduction. Cambridge: Harvard University Press.

Griessler, E., & Hager, M. (2017). Changing Direction: The Struggle of Regulating Assisted Reproductive Technology in Austria. Reproductive Biomedicine online, 22;3:68-76. doi: 10.1016/j.rbms.2016.12.005.

Habermas, J. (2003). The Future of Human Nature. Cambridge: The translation polity press.

Hammarberg, K., Kirkman, M., & de Lacey, S. (2016). Qualitative Research Methods: When to Use Them and How to Judge Them. Human Reproduction, 31, 3, 498–501, doi: 10.1093/humrep/dev334.

Harmon, S. H. (2016). Modernizing Biomedical Regulation: Foresight and Values in the Promotion of Responsible Research and Innovation. Journal of Law and the Biosciences, 680–686, doi: 10.1093/jlb/lsw053.

Harris, J. (2007). Enhancing Evolution, The Ethical Case of Making Better People. New Jersey: princeton University Presss.

Hashiloni-Dolev, Y., & Raz, A. E. (2010). Between Social Hypocrisy and Social Responsibility: Professional Views of Eugenics, Disability and Repro-Genetics in Germany and Israel. New Genetics and Society, 29(1) 187–102, doi: 10.1080/14636770903561364.

Hashiloni-Dolev, Y., Kaplan, A., & Shkedi-Rafid, S. (2011). The Fertility Myth: Israeli Students' Knowledge Regarding Age-Related Fertility Decline and Late Pregnancies in an Era of Assisted Reproduction Technology. Human Reproduction, 11, 3045-53, doi: 10.1093/humrep/der304.

Health Ministry of Israel. (2018). In Vitro Fertilization (IVF) Treatments 1990-2016. Israel: Facilities and Equipment Licensing Division, Health Information Division, https://www.health.gov.il/PublicationsFiles/IVF1990_2015.pdf.

Inhorn, M. C., & Patrizio, P. (2015). Infertility Around the Globe: New Thinking on Gender, Reproductive Technologies and Global Movements in the 21st Century. Human Reproduction Update, 21, 4, 411–426, doi: 10.1093/humupd/dmv016.

Ishihara, O. e. (2019). Assisted reproductive technology in Japan: A summary report for 2016 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol., 1, 7–16, doi: 10.1002/rmb2.12258.

Jiahua, J., Xiangbin, Y., Yijun, L., & Yumei, L. (2016). How users adopt healthcare information: An empirical study of an online Q&A community. International Journal of Medical Informatics, 86, 91–103, doi: org/10.1016/j.ijmedinf.2015.11.002.

Johnson, M., & Petersen, K. (2008). Public Interest or Public Meddling? Towards a Subjective Framework for the Regulation of Assisted Reproduction Technologies. Human Reproduction, 3, 716-28, doi: 10.1093/humrep/dem387.

Jonas, H. (1984). The Imperative of Responsibility. University of Chicago.

Klitzman, R. (2008). Anticipating Issues Related to Increasing Preimplantation Genetic Diagnosis Use: A Research Agenda. Reproductive BioMedicine Online, 17, 1, 33-42, doi: 10.1016/S1472-6483(10)60188-5.

Knoepfler, P. (2016). GMO Sapiens, The Life-Changing Science of Designer Babies. Singapore: World Scientific Publishing.

Krimsky, S. (2019). Ten Ways in Which He Jiankui Violated Ethics. Nature Biotechnology, 37, 19, doi: org/10.1038/nbt.4337.

La Marca, A., & Sunkara, S. K. (2014). Individualization of Controlled Ovarian Stimulation in IVF Using Ovarian Reserve Markers: From Theory To Practice. Human Reproduction Update, 20(1), 124-40, doi: 10.1093/humupd/dmt037.

Landeta, J. (2002). El Método Delphi, Una téecnica de previsión del futuro. Barcelona: Ariel.

Landeta, J., & Barrutia, J. (2011). People Consultation to Construct the Future: A Delphi Application. International Journal of Forecasting, 27(1), 134–151, doi: .org/10.1016/j.ijforecast.2010.04.001.

Landeta, J., J., M., Ruíz, V., & Galter, J. (2008). Results of a Delphi Survey in Drawing Up the Input–Output Tables for Catalonia. Technological Forecasting & Social Change, 75(1), 32–56, doi: org/10.1016/j.techfore.2007.01.005.

Lewis, C. S. (1943). The Abolition of Man. New York: Oxford University Press.

Lippman, A. (1991). Prenatal Genetic Testing and Screening: Constructing Needs and Reinforcing Inequities. American Journal of Law and Medicine, 17(1-2):15-50.

Lock, S. (1990). Towards a National Bioethics Committee. British Medical Journal, 300, 1149-1150, doiI: 10.1136/bmj.300.6733.1149.

Lu, L., Lv, B., Huang, K., Xue, Z., Zhu, X., & Fan, G. (2016). Recent Advances in Preimplantation Genetic Diagnosis and Screening. Journal of Assisted Reproduction and Genetics, 33, 9,1129–1134, doi: 10.1007/s10815-016-0750-0.

Machado, M. P., & Galdeano, A. S. (2011). Coverage of Infertility Treatment and Fertility Outcomes: Do Women Catch Up? Bonn, Germany: IZA Discussion, Paperhttp://ftp.iza.org/dp5783.pdf.

Martin, L. J. (2014). The World's Not Ready for This: Globalizing Selective Technologies. Science, Technology, & Human Values, 39(3), 432-455, doi: 10.1177/0162243913516014.

Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS Medicine, 9(12), e1001356. doi: 10.1371/journal.pmed.1001356.

Milachich, T. (2014). New Advances of Preimplantation and Prenatal Genetic Screening and Noninvasive Testing as a Potential Predictor of Health Status of Babies. BioMed Research International, 306505. doi: 10.1155/2014/306505.

Murphy, T. (2014). Im Defence of Prenatal Genetic Interventions. Bioethics, 28(7), 335-42, doi: 10.1111/j.1467-8519.2012.02009.x.

Nemet, G. F. (2009). Demand-Pull, Technology-Push, and Government-Led Incentives for Non-Incremental Technical Change. Research Policy, 38(5) 700–709, doi: 10.1016/j.respol.2009.01.004.

Nuffield Council on Bioethics. (2018). Genome Editing and Human Reproduction: Social and Ethical Issues. London.

Okoli, C., & Pawlowski, S. D. (2004). The Delphi Method as a Research Tool: An Example, Design Considerations and Applications. Information & Management, 42(1), 15–29, doi: 10.1016/j.im.2003.11.002.

Orvieto, R., & Gleicher, N. (2016). Should Preimplantation Genetic Screening (PGS) be Implemented to Routine IVF Practice? Journal of Assisted Reproduction and Genetics, 11, 1445-1448, doi: 10.1007/s10815-016-0801-6.

Palermo, G. D., Neri, Q. V., Takeuchi, T., & Rosenwaks, Z. (2009). ICSI: Where We Have Been and Where We Are Going. Seminars in Reproductive Medicine, 2, 191-201, doi: 10.1055/s-0029-1202309.

Paraskevopoulou, E. (2012). Non-Technological Regulatory Effects: Implications for Innovation and Innovation Policy. Research Policy, 41,6, 1058– 1071, doi: org/10.1016/j.respol.2012.03.018.

Pavone, V., & Arias, F. (2012). Beyond the Geneticization Thesis: The Political Economy of PGD/PGS in Spain. Science, Technology, & Human Values, 37(3) 235-261, DOI: 10.1177/0162243911411195.

Ramsey, P. (1972). Shell we "Reproduce"? JAMA, 220 (10), 1346-1350; (11), 1481-1485.

Ravitsky, V. (2002). Genetics and Education: The Ethics of Shaping Human Identity. Mount Sinai Journal of Medicine, 69(5):312-6.

Ribeiro, B. E., & Quintanilla, M. A. (2015). Transitions in Biofuel Technologies: An Appraisal of the Social Impacts of Cellulosic Ethanol Using the Delphi Method. Technological Forecasting & Social Change, 92, 53–68, do: 10.1016/j.techfore.2014.11.006.

Rogers, E. M. (1983). Diffusion of Innovation. New York: The Free Press.

Rommetveit, K. (2011). Genetic Enhancement, Futures Tense. Futures, 43, 76–85, doi: 10.1016/j.futures.2010.10.014.

Sandel, M. J. (2004). The Case Against Perfection. The Atlantic, 293, 3, 51-62.

Savulescu, J. (2001). Procreative Beneficence: Why We Should Select the Best Children? Bioethics, 15(5-6), 413-26, doi: 10.1111/1467-8519.00251.

Second International Summit on Human Genome Editing. (2018a). Genes, Genomes, and Genetic Variation. (pp. Day 1, Session 1). Hong Kong: The National Academies of Sciences Engineering Medicine, http://www.nationalacademies.org/gene-editing/2nd_summit/first_day/index.htm.

Second International Summit on Human Genome Editing. (2018b). Global Perspectives: Somatic and Germline Therapy, Prevention, and Enhancement Applications, Identifying Basic Principles for Moving Forward. (pp. Day 3, Session 1, and 2). Hong Kong: The National Academies of Sciences Engineering Medicine, http://www.nationalacademies.org/gene-editing/2nd_summit/third_day/index.htm.

SEF. (2016). Registro Nacional de Actividad - Técnicas de Reproducción Asistida, Informe estadístico de Técnicas de Reproducción Asistida 2016.
https://www.registrosef.com/public/docs/sef2016_IAFIVm.pdf: Sociedad Española de Fertilidad.

Shulman, C., & Bostrom, N. (2014). Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer? Global Policy, 5(1) 85-92, doi: 10.1111/1758-5899.12123.

Silver, M. L. (1997). Remaking Eden: How Genetic Engineering and Cloning Will Transform the American Family. New York: Harper Perennial.

Skirton et al. (2013). A Delphi Study to Determine the European Core Curriculum for Master Programmes in Genetic Counselling. European Journal of Human Genetics, 21, 1060–1066, doi: 10.1038/ejhg.2012.302.

Sobotka, T. (2016). Childlessness in Europe: Reconstructing Long-Term Trends Among Women Born in 1900–1972. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 17-50). Berlin: Springer Open.

Spar, L. D. (2006). The Baby Business, How Money Science, and Politics Drive the Commerce of Conception. Boston, Massachusetts: Harvard Business School Press.

Swanson, A., Lau, E., & Strawn, E. (2007). Preimplantation Genetic Diagnosis: Technology and Clinical Applications. Wisconsin Medical Journal, 106(3):145-51.

Tarkkala, H., Helén, I., & Snell, K. (2018). From Health to Wealth: The Future of Personalized Medicine in the Making. Futures, doi: org/10.1016/j.futures.2018.06.004.

Von der Gracht, H. A. (2012). Consensus Measurement in Delphi Studies Review and Implications for Future Quality Assurance. Technological Forecasting & Social Change, 79(8), 1525–1536, doi: 10.1016/j.techfore.2012.04.013.

Wailoo, K., & Pemberton, S. (2006). The Troubled Dream of Genetic Medicine. Baltimore: The Johns Hopkins University Press.

Walsh, V. (1983). Invention and Innovation in the Chemical Industry: Demand-Pull or Discovery-Push? Research Policy, 13(4) 211-234, doi: 10.1016/0048-7333(84)90015-5.

Wang, Z. (2014). Automatic Zona Pellucida Dissection Position Selection for Embryo Biopsy in Pre-implantation Genetic Diagnosis. International Conference on Robotics and Biomimetics (pp. 475-480). Bali: IEEE.

Zlotogora, J. (2014). Genetics and Genomic Medicine in Israel. Molecular Genetics & Genomic Medicine, 2(2): 85–94, doi: 10.1002/mgg3.73.

Zuckerman, S., Zeevi, D. A., Gooldin, S., & Altarescu, G. (2017). Acceptable Applications of Preimplantation Genetic Diagnosis (PGD) among Israeli PGD Users. European Journal of Human Genetics, 25, 1113–1117, Doi: 10.1038/ejhg.2017.113.

5. CONCLUSIONS AND POLICY IMPLICATIONS

This thesis aimed to provide a more accurate understanding of the diffusion process of Assisted Reproductive Technologies (ART), including their trajectories, opportunities, limitations, and policy implications.

First, through a technology and demand forecast for the following 20 years, as presented in chapter 2 and further developed in chapter 4, we assist in reducing the gap derived from asymmetries in technoscientific knowledge between ART and the socio-ethical literature. Our forecasting provides a more realistic insight towards the potentials and limitations of ART in general, and in Israel and Spain in particular.

Second, a regulatory assessment of the current state of affairs in Israel and Spain, presented in chapter 3, provides both a general analytical framework for cross-country analysis and a case-study comparison between two leading ART industries. It assists in understanding better the factors affecting regulation and priority setting, and thus in interpreting the differences between countries. Moreover, it allows analyzing strengths and flaws of ART regulations, as well as identifying risks which may arise or extend from the expected growth of the ART industry.

Third, building on our analysis in chapter 2, and combining it with experts' attitudes towards the regulation of reproductive genetics extracted from the second Delphi, we assess the market and regulatory trends that may (or not) lead to the geneticization of reproduction. This analysis, presented in chapter 4, is the most far-reaching and speculative element of this thesis, in which we present possible scenarios for a geneticization or medicalization process in human reproduction. Chapter 4 introduces an approach to the diffusion of medical innovations based on supply, demand, and regulations, which may serve for future studies in other medical fields.

Technology forecast: We may expect a significant increase in IVF birth rates for the next 20 years towards 50%, mainly resulted from improvements in the stages of egg fertilization and embryo implantation. However, we noted some doubts about the possibility of significantly increasing the number of extracted eggs, which could remain the scarcest resource in IVF treatment. It seems that the most expected improvements are related to equipment and clinic quality control, as average-budget clinics would close the gap with today's premium ones, suggesting that IVF is evolving from a "pre-paradigmatic stage" to a "paradigmatic stage", where a generally accepted scientific approach is gaining ground (Teece, 1986).

The selection of embryos by genetic screening (PGS) is projected to improve and become more useful. The experts also raised high expectations for improvement in genomics, allowing better identification of the relationship between genes and various multifactorial diseases. Therefore, following an increase in the practice of PGS, PGD will also become more common, although a larger potential, particularly in the long run, was attributed to genetic engineering by CRISPR/CAS.

Attitudes towards the regulation of reproductive genetics: The experts from both Delphi surveys approved any use of ART, given that it is safe and provide significant health benefits. The physicians have drawn a clear line between allowing the use of PGD for multifactorial diseases and banning it for non-medical reasons. Conversely, the "bioethics panels" from the second Delphi did not draw a clear line, but marked a grey-zone of regulation, concerning treatments of which health benefits are not yet clear, including the use of CRISPR/CAS, PGS for chromosome abnormalities or whole-exome screening, and the use of PGD for multifactorial diseases.

It seems that the central dilemma on the regulatory agenda is whether or not these technologies may medically benefit the patient. It was neither the slippery slope argument nor any moral or ethical concern regarding the social consequences of reproductive genetics, although the experts were careful and attentive to those issues.

The first stage of diffusion: The panel of physicians anticipated that, within 20 years, the share of IVF births in Israel and Spain would be around 14% and 19%, respectively. This forecast is not surprising, considering that many studies estimated that infertility affects up to 15% of the population (Evers, 2002; Spar, 2006; Agarwal et al., 2015; ASRM, 2015), and that this share may be growing due to the rising age of parenthood, environmental factors, lifestyle and social reasons (Boivin et al, 2007; Mascarenhas et al., 2012; Johnson, 2014; Inhorn & Patrizio, 2015; Sobotka, 2016).

The panel also forecasted that PGD would growingly be a factor which increases demand for IVF and, more importantly, that it will become an add-on to IVF in about 40% of the cycles, in contrast to a much smaller share today (less than 5%). Also, at this stage of diffusion, CRISPR/CAS will be introduced as a more practical, efficient, and potent technology. Nevertheless, it may be a long and gradual process and, even after its first applications, preoccupations with safety and adverse effects will take time to dissolve. Hence, the use of CRISPR/CAS could, for an extended period, be limited to single-gene disorders and a few more conditions of limited complexity (Evitt et al., 2015; Nuffield Council on Bioethics, 2018).

The implementation of the first stage: Israel and Spain are among the heaviest consumers of IVF due to various factors of which the most central is age-related infertility. In Spain, this trajectory has been described as "structural infertility" (Marre, 2009; Marre et al., 2018). It relates to socio-financial conditions that are leading many women and men to postpone parenthood to an age in which ART is often needed, and most likely requires donor-eggs. In Israel, cultural, political, and social environments are shaping public views on infertility, ART, and genetic relatedness. Thus, Israelis are repeating many IVF cycles, which are publicly funded until the age 44, attempting to fulfill their desire to form large families by giving birth to genetically related children (Birenbaum-Carmeli & Dirnfeld, 2008; Birenbaum-Carmeli, 2010).

The prevalence of donor-eggs as a solution to infertility is a significant and growing matter in Spain, which is already among the largest producer of such donations in the world. Albeit, it is also a growing phenomenon in Israel, although most donations are coming from abroad. The market for eggs raises many ethical controversies, concerning the physical and emotional burden on female donors and the limitation on reimbursement for donations in comparison with the multiplied profit generated by intermediaries. Moreover, within a few decades, hundreds of thousands of people (also due to sperm donation) will have no access to one or both of their biological parents' genetic information, medical history, and identity. It may provoke great disadvantage, both psychological and medical, considering the growing weight of genomics and precision medicine.

Another controversial issue in both countries is the practice of PGS, a relatively new technology. Its efficiency is not yet proven; it is not publicly funded and is being offered as an add-on, providing large profits to clinics. Nevertheless, the use of PGS involves taking a biopsy from an embryo, which may as well pave the way to a significant increase in the use of PGD, by turning the screening for chromosomal abnormalities into a screening of large parts (or the whole) of the exome to detect mutations.

The second stage of diffusion: At this stage, the only growth channel left for the ART industry is reproductive genetics, i.e., IVF dedicated for PGD or CRISPR/CAS. According to our findings from chapter 4, both panels strongly opposed the use of reproductive genetics for detecting desired physical and cognitive traits. The moral bases for this opposition could slowly be altered, affected by a spiral-shaped process in which technological development and values drive one another (Beck-Gernsheim, 2000). However, as long as this attitude holds, the only way for the industry to attract a larger share of the public would be by delivering (or, otherwise, promising) significant health benefits

to people born by ART. Nevertheless, most babies born today are healthy, and most adult people live healthy lives, at least until oldness. Could reproductive genetics deliver babies who would suffer less multifactorial aging-associated diseases? Could such a promise appeal to the majority of the human population?

In the long run, a full medicalization of reproduction based on geneticization could be realized, but the true potential of genomics is still foreign to us. We may very soon be able to cut and paste DNA segments of the human embryo in a swipe of a hand. Conversely, it will take much longer to fully understand genomics and the epigenetic implications of CRISPR/CAS. Reproductive genetics could also end up being a matter of choice between various alternatives concerning the genetic composition of an embryo, due to gene pleiotropy (Nuffield Council on Bioethics, 2018). Most importantly, the human lifecycle is long, and proofing the benefits of reproductive genetics aiming at multifactorial late-onset diseases will require the conduction of follow-up throughout the adult lives of ART babies. Of course, with the lack of full evidence, the market forces may induce scientific speculations, beliefs, and expectations, with socio-technical imaginaries generating perceived benefits of geneticization.

Policy implications: This study has concluded that the medicalization of reproduction is a long and observable process and that the geneticization thesis will most likely not be realized due to a moment of breakthrough (Brown & Michael, 2003) in a particular research project of some institution or an enterprise. Alternatively, it will take the form of a spiral shaped-process, driven by the gears of market forces, private interests, trends nourished by socio-technical imaginaries and shifts in regulation. Such a process is not necessarily good or bad, but it is recommended to observe it and follow it, and also to attempt to influence and direct it to the benefits of society by means of both national and international regulation. Our “bioethics panels” were preoccupied with the large influence of commercial interests on regulations in contrast to a weak influence of ethical interests and health considerations. Regardless of the difference in the shares of private/public funding between the countries, in both markets, demand is, to some extent, induced by private interests.

Our analysis raises that, despite the large economic benefits of the ART industry, governments should aspire to slow down the medicalization process. First, by distributing accurate information regarding both ART and infertility through available means (such as the media, education and health systems). We also advise regulators to carefully supervise the information delivered to the public by private clinics. The field is complex and involves large profits, meaning that the accuracy of the information should not be taken for granted, particularly when it comes to reproductive genetics for multifactorial diseases.

Second, ART is not necessarily the optimal or only solution; other alternatives should be considered. Epidemiological research about infertility resulting in prevention should be a priority and should receive more resources. A further focus should be given to transparency, which could be done by improving national registries and increasing their scope, providing more details regarding clinical diagnosis, separating between PGD and PGS as two techniques with different aims, and adding economic dimensions, such as average costs, or private and public distribution analysis.

Third, it is also important to realize that the medicalization process of reproduction is largely due to social trends since the modern lifestyle is driving the postponement of parenthood. An inclusive societal debate should deal with the adequacy (or inadequacy) of ART to solve such problem, in light of other social solutions based on welfare policies. As fertility preservation is already becoming a trend, we should cautiously test some other non-medical alternatives.

Fourth, our analysis questions the institutional setting and recommends to observe the alternative of non-governmental statutory central regulatory agencies to regulate ART. Noticing the insufficient regulatory response to the first stage of diffusion concerning aspects of financial interest, disinformation and the pace of medicalization, we may greatly doubt whether Israel, Spain or any other country are ready to welcome the second stage. It leads us to the importance of international debate, which should result in regulatory collaboration, particularly regarding the use of advanced reproductive genetics. When CRISPR/CAS design artists offer their services, state borders and national regulations will play a very limited role (see also Martin, 2014).

In sum, regulators should avoid “sleepwalking” into this process by allowing uncontrolled technological momentum (Nuffield Council on Bioethics, 2018), though our moral dimensions should also not be based on outdated or misleading contexts, which would lead to inflated hopes or dystopian theories. Alongside with the medicalization of reproduction, an open debate must regularly address questions of freedom of choice and personal autonomy in decision making, while being regularly updated according to the most realistic and accurate scientific context.

Future research agenda

A recommendation for further studies includes the approach to other countries in search of other evidence for the emerging medicalization process and regulatory deficiencies. Particularly, we identify potential interest in the largest and most fast-developing markets in the world, such as Japan, the U.S., China, India, France, Australia, the U.K., and Denmark. Regarding some of these countries, there might be considerable interest in identifying inequalities in access to services and their implications.

It would also be interesting to study other institutional settings, based on non-governmental statutory central regulatory agency, in order to search for a more adequate solution to ART regulation, providing useful insights regarding regulatory frameworks and their true potential. Finally, it would be interesting to approach the demand-side through patients by other methods which may require further research resources but could provide some very important perspectives. For example, by interviewees and surveys, focusing on the factors that create inequality in access, and the possible reasons that may drive patients to approach reproductive genetics, as well as the moral limits they place for such approach, and how these limits may shift along time.

References:

Agarwal, A., Mulgund1, A., Hamada, A., & Chyatte, M. R. (2015). A Unique View on Male Infertility Around the Globe. Reproductive Biology and Endocrinology, doi 10.1186/s12958-015-0032-1.

ASRM, P. C. (2015). Diagnostic evaluation of the infertile male: a committee opinion. Fertility and Sterility, 103(3), e18-25. doi: 10.1016/j.fertnstert.2014.12.103.

Beck-Gernsheim, E. (2000). Health and Responosibility: From Social Change to Technological Change and Vice Versa. In B. Adam, U. Beck, & J. Van Loon, The Risk Society and Beyond: Critical Issues for Social Theory (pp. 122-134). London: Sage.

Birenbaum-Carmeli, D. (2010). Genetic Relatedness and Family Formation in Israel: Lay Perceptions in the Light of State Policy. New Genetics and Society, 29, 1, 73–85, doi: 10.1080/14636770903561380.

Birenbaum-Carmeli, D., & Dirnfeld, M. (2008). In Vitro Fertilisation Policy in Israel and Women's Perspectives: The More the Better? Reproductive health matters, 16(31):182–191, doi: 10.1016/S0968-8080(08)31352-4.

Boivin, J., Bunting, L., A. Collins, J., & Nygren, K. G. (2007). International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. Human Reproduction, 22, 6. 1506–1512, doi: 10.1093/humrep/dem046.

Brown, N., & Michael, M. (2003). A Sociology of Expectations: Retrospecting Prospects and Prospecting Retrospects. Technology Analysis & Strategic Management, 15:1, 3-18, doi: 10.1080/0953732032000046024.

Evers, J. L. (2002). Female Subfertility. The Lancet, 13; 360(9327), 151-9, doi: 10.1016/S0140-6736(02)09417-5.

Evitt, N. H., Mascharak, S., & Altman, R. B. (2015). Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework. The American Journal of Bioethics, 15(12): 25–29, doi: 10.1080/15265161.2015.1104160.

Inhorn, M. C., & Patrizio, P. (2015). Infertility Around the Globe: New Thinking on Gender, Reproductive Technologies and Global Movements in the 21st Century. Human Reproduction Update, 21, 4, 411–426, doi: 10.1093/humupd/dmv016.

Johnson, L. (2014). Regulation of Assisted Reproductive Treatment (ART) in Australia & Current Ethical Issues. Indian Journal of Medicine Research, 140, 9-12.

Marre, D. (2009). The silences of the Spanish Adoption. Revista de Antropología Social, 18 97-126, http://www.redalyc.org/articulo.oa?id=83817222006.

Marre, D., San Román, B., & Guerra, D. (2018). On Reproductive Work in Spain: Transnational Adoption, Egg Donation, Surrogacy. Medical Anthropology, 37, 2, 158–173, doi: org/10.1080/01459740.2017.1361947.

Martin, L. J. (2014). The World's Not Ready for This: Globalizing Selective Technologies. Science, Technology, & Human Values, 39(3), 432-455, doi: 10.1177/0162243913516014.

Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLOS Medicine, 9(12), e1001356. doi: 10.1371/journal.pmed.1001356.

Nuffield Council on Bioethics. (2018). Genome Editing and Human Reproduction: Social and Ethical Issues. London.

Sobotka, T. (2016). Childlessness in Europe: Reconstructing Long-Term Trends Among Women Born in 1900–1972. In M. Kreyenfeld, & D. Konietzka, Childlessness in Europe: Contexts, Causes, and Consequences (pp. 17-50). Berlin: Springer Open.

Spar, L. D. (2006). The Baby Business, How Money Science, and Politics Drive the Commerce of Conception. Boston, Massachusetts: Harvard Business School Press.

Teece, D. J. (1986). Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy. Research Policy, 15(6), 285-305, doi: 10.1016/0048-7333(86)90027-2.

ANNEX 1 - DELPHI QUESTIONNAIRE 1

Name:

Country:

Expertise

☐ IVF ☐ PGD ☐ IVF+PGD

Years of experience:

IVF

For questions 1-7 please try to avoid any considerations of ethics, costs, policies etc. Analyze the questions within a mere techno-scientific view.

1. Oocytes – What is the potential impact of these technologies to improve quality and increase the number of available retrieved oocytes over the next 20 years?

(On a scale of 1- No impact, 10- very high impact, No Answer-Not familiar)

	1	2	3	4	5	6	7	8	9	10
IVF augment - using the mitochondria from egg precursor (EggPC) cells to supplement the existing mitochondria in the eggs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improvement of Hormone Replacement Therapy (HRT) and Oocyte Retrieval (OCR) methods	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oocyte cryopreservation - retrieval, freezing and accumulation since a young age	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
In-Vitro Maturation (IVM)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Oocyte Donation with Mitochondrial Manipulation Technology (MMT) - to replace eggs from older patients with eggs from younger donors	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Growing oocytes from stem cells	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ovarian tissue cryopreservation at a young age to be transplanted later	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

2. Embryos - What is the potential impact of these technologies to improve quality and increase the number of returnable embryos over the next 20 years?

(On a scale of 1- No impact, 10- very high impact, NA-Not familiar)

	1	2	3	4	5	6	7	8	9	10
Improved fertilization methods - better ICSI or better IVF	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Introduction of robotic technologies into the industry - replace the human hand by a more accurate mechanism	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Quality Improvement and quantity increase of oocytes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improved clinic quality control - noise, pollution, sterility, etc.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
More advanced incubators and temperature regulation - Optimal embryo culture environment	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improved methods of sperm selection IMSI/PICSI/SAT/MACS/SCSA	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sperm enhancement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

3. Pregnancy and birth rates - A. What is the potential impact of these technologies to increase implantation and live-birth rates over the next 20 years?

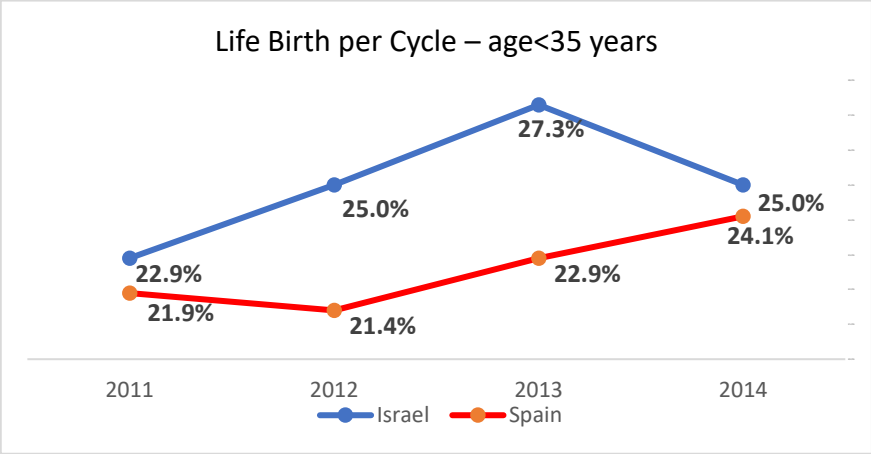
(On a scale of 1- No impact, 10- very high impact, NA-Not familiar)

	1	2	3	4	5	6	7	8	9	10
Improved PGS technologies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improved clinic quality control - noise, pollution, sterility, etc.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improved incubators and temperature regulation - optimum embryo culture environment	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Quality Improvement and quantity increase of embryos	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Improved methods of transplantation – timing and location	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Introduction of robotic technologies into the industry – to replace the human hand with a more accurate mechanism	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Introduction of Artificial Intelligence (classification models) - to identify the best embryos	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

4. Pregnancy and birth rates.



Consider IVF in general, how do you predict live birth rate per cycle for woman younger than 35 years, in your country (in percentage):

In 10 years?

In 20 years?

You may also add a comment:

Genetics

5. Multifactorial diseases and characteristics - How do you predict that the ability to identify correlations between genes and the following disorder and characteristics categories, will improve over the next 20 years?

(on a scale of 1-No progress to 10- Very high progress)

	1	2	3	4	5	6	7	8	9	10
Cancerous diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cardiovascular diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Neurological disorders	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Metabolic diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Eye/Skin/Hair Color	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Height/body type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tendency for obesity	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Memory/intelligence/other cognitive traits	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tendency for addictions	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

6. Genetic Engineering - How do you assess the probability that within 20 years, the technology will be available to safely engineer embryos providing the following features?

(On a scale of 1- Not at all probable, 10-Extremely probable)

	1	2	3	4	5	6	7	8	9	10
Gene replacements	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fixing parts of chromosomes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Removal of multifactorial genetic disorders	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Editing traits of appearance and body type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cognitive enhancement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

7. Please consider the technological progress regarding the methods mentioned in questions 1 and 2 and think about the following scenario:

An IVF is carried out in order to conduct a multiple-factor PGD (searching for monogenetic and multifactorial disorders such as cancerous/cardiovascular/neurological diseases and other genetic traits, all at once) where the aim is to obtain as many embryos as possible in order to enable a broad selection.

The patient is healthy and was planning to have such a selection for some reasonable period of time with a reasonable number of cycles (reasonable in your opinion).

On a scale of 1- Not at all probable, 10-Extremely probable, what is the probability that in 20 years a standard patient will have:

	1	2	3	4	5	6	7	8	9	10
more than 50 embryos for selection?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
more than 100 embryos for selection?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
more than 150 embryos for selection?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

You may also add a comment:

Socio-Political

8. Government Regulations - How do you assess doctors and government's willingness to permit and finance the following procedures in the next 20 years?

* Consider also the governance ability regarding regulation and inclusion of these services in the public health.

(On a scale of 1- Not at all probable, 10-Extremely probable)

	1	2	3	4	5	6	7	8	9	10
Allow PGD for cancerous diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for cancerous diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow PGD for cardiovascular diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for cardiovascular diseases	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow PGD for neurological disorders	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for neurological disorders	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow PGD for eye/skin/hair color	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for eye/skin/hair color	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow PGD for physical traits (e.g. height, athleticism, tendency for obesity)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for physical traits (e.g. height, athleticism, tendency for obesity)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow PGD for intellectual and cognitive characteristics (e.g. memory, intelligence)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance PGD for intellectual and cognitive characteristics (e.g. memory, intelligence)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Allow Genetic engineering in human beings	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Finance Genetic engineering in human beings	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

You may also add a comment:

9. Impact on inequalities - How would the advantage of a “genetically selected person” compared to a “non-selected person” be expressed in 20 years?

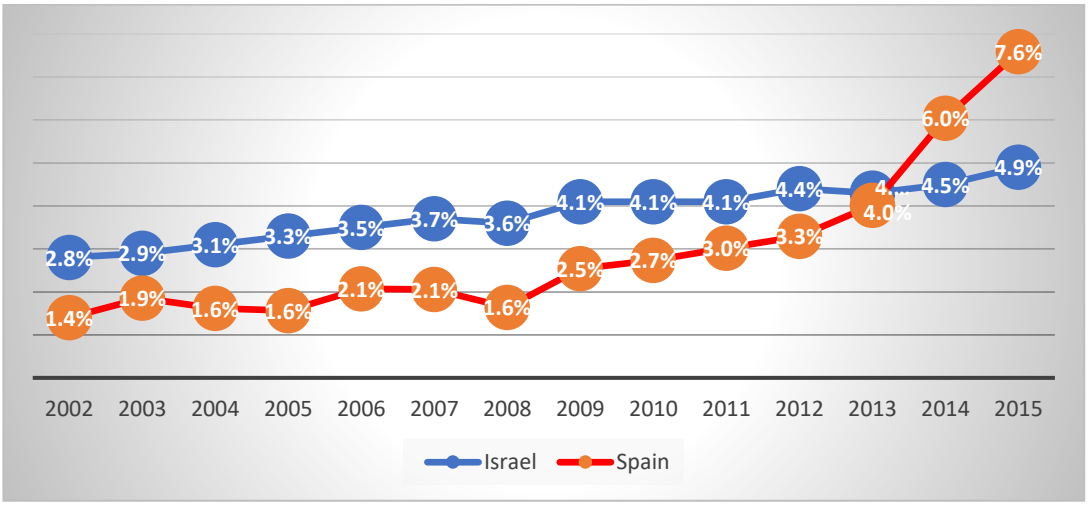
(On a scale of 1-No advantage, 10-Very significant advantage)

	1	2	3	4	5	6	7	8	9	10
In childhood (regarding diseases)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
In the late stages of life (Cancer, Alzheimer etc.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Throughout life (better overall health)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Physical traits - Appearance and body type	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intellectual and cognitive characteristics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Others (if you add an option please rate it from 1 to 10)

You may also add a comment:

10. Demand for IVF -



In 2014 PGD was performed in less than 5% of IVF treatment in Spain, and not more than 10% in Israel (Estimation).

Please estimate the IVF share of total birth in your country (In percentage) in 20 years from today:

Please estimate, what percentage of IVF treatment will include PGD or any genetic testing/screening which aims to identify disorder/diseases or traits (in contrast to the current use of PGS) in your country in 20 years?

You may also add a comment:

11. What might be the main cause for increase in the use of IVF?
(Rank by order of relevance)

- [ ] Decreased fertility due to aging (a demand for late pregnancies, including oocyte donation)
- [ ] Decreased fertility due to lifestyle and environmental hazards
- [ ] Increased demand for PGD
- [ ] Genetic Engineering
- [ ] Increased demand for sperm donation

Others (if you add an option please rank it from 1 to 6)
You may also add a comment:

ANNEX 2 - DELPHI QUESTIONNAIRE 2

1. Actual vs. optimal influence of different factors on ART regulations

Please rate the **optimal** level in which you believe that the following factors should affect regulations of In Vitro Fertilization (IVF).

In comparison, please also rate the actual level in which, according to your perception, these factors **actually** affect regulation of IVF in your country:

On a scale of: 1 – (Very low impact) to 10 – (Very high impact)

a. Patient's health, clinical safety.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

b. Scientific evidence for the success rates of the treatments.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

c. National fertility rates.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

d. Budgetary constraints of healthcare system.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

e. Freedom of commercial activities and the private sector's interest.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

f. Justice and equity of access

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

g. Patients' autonomy to make their own choices.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

h. Protect vulnerable individuals from exploitation.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

i. Public's values and perceptions.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

j. Global trends and guidelines of regulatory affairs professional societies in the field.

Optimal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Actual	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Comments:

2. Satisfaction with outcome from regulation

Regarding each of the following categories, please rate your level of **satisfaction** with the outcome of regulation in your country (please consider results of the law and its enforcement combined).

On a Scale of: 1- (Very unsatisfied) to 10 – (Very Satisfied)

a. Public clinics' capacity to respond to the demand.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

b. Eligibility criteria for public funding of IVF.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

c. Limits on private clinics providing services.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

d. Clinics' good practices, safety, proper diagnosis etc.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

e. The regulations on imbursements for gametes.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

f. Registry of gametes and embryos donors.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

g. Anonymity of gametes and embryo donors.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

h. Eggs-vitrification for social egg freezing.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

i. Preimplantation Genetic Diagnosis (PGD).

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

j. Gestational Carriers / Surrogacy.

Satisfaction	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Comments:

3. Measures to prevent and cure infertility

How should the public sector approach the average increase in infertility and demand for IVF?

Please consider the following options:

On a scale of 1 - strongly opposed to 10 – strongly support.

a. Increasing the supply and/or efficiency of publicly provided IVF to reduce waiting lists and inequity.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

b. Funding (fully or partially) fertility preservation by freezing gametes.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	1 ☐

c. Increasing the supply of donor eggs by funding it.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

d. Securing proper diagnosis of infertility before referring to IVF.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

e. Funding more research regarding environmental causes of infertility.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

f. Dedicating more resources to reduce environmental factors and cure/prevent diseases causing infertility.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

g. Distributing accurate information regarding age implication and environmental factors on infertility and success rates of assisted reproductive medicine (ART) via public-health campaigns in education system, thru family doctors and the media.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

h. Increasing social support policies to facilitate parenting at younger age.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

i. The public sector should minimize its intervention in this issue.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Comments:

4. – General attitudes towards the regulation of PGD

What is your opinion regarding the following statements?

On a scale of 1 – Completely disagree to 10 – Completely agree.

a. The public sector should aim at reducing regulations regarding PGD to a minimum in-order to allow the patients maximum free choice.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

b. When PGD is already done for medical reasons, sex selection as an add-on service should be allowed. In-other words, the doctor may reveal the sex of the (clinically) selected embryos allowing the patients to choose sex, if it doesn't interrupt with the treatment.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

c. When IVF is already performed due to infertility, regulation should be more tolerant towards PGD, it should be allowed as an add-on service to IVF for some range of disorders.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

d. It is viable in terms of regulations to separate between the use of Preimplantation Genetic Screening (PGS - screening for chromosomal abnormality) and the use of PGD for detecting disorders. In other words, in case PGS will eventually become a very common add-on for IVF cycles with the aim to increase the prospects of the treatment, regulations may still prevent the clinics from regularly using the biopsies taken for PGS to perform PGD.

1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Comments:

5. Regulation of specific practices of reproductive genetics

Would you advise the public sector to allow the following procedures (in case the technology will provide efficiency and safety)?

Would you advise the public sector to fund the following procedures?

On a scale of: 1 – Completely opposing to 10 – Completely supporting.

a. PGD for severe monogenetic disorders of early-onset and high-level of penetrance with no simple cure.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

b. PGD for severe monogenetic disorders of medium-late-onset and high-level of penetrance with no simple cure.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

c. PGD for severe monogenetic disorders of medium-late-onset and medium level of penetrance with no simple cure.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

d. PGD for multifactorial diseases, (cancerous/ metabolic/ cardiovascular/ neurological) with medium-late-onset and medium level of penetrance.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

e. PGS for detection of chromosomal abnormalities, in-order to increase the prospects of an IVF treatment.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

f. PGS with whole exome screening.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

g. GE (CRISPR) for severe monogenetic disorders of early-onset and high-level of penetrance with no simple cure in case PGD didn't provide solution.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

h. PGS for social sex selection.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

i. PGD for physical traits selection.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

j. PGD for cognitive characteristics selection.

Allow	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Fund	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Comments: