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ASSISTED REPRODUCTION TECHNOLOGIES

Regulatory responses to assisted reproductive technology: a comparative analysis of Spain and Israel

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Abstract

Purpose The market of assisted reproductive technologies (ARTs) is rapidly evolving, raising growing ethical and social dilemmas. This paper compares the regulatory responses to technological and market developments in Israel and Spain, both intensive users of ART. We identify strengths and deficiencies in the regulation of ART in these two countries.

Methods We developed a conceptual framework to classify the factors affecting regulations and priority setting, and applied it using a Delphi survey combined with in-depth interviews. We selected two panels of experts from various fields, trying to simulate the bioethics committees of Israel and Spain.

Results ART is often wrongfully perceived as a solution to age-related infertility. Both panels embraced alternative solutions. The impact of private commercial interest on regulations is resulting in excessive practices such as the repeat of ineffective cycles and the push of sometimes unnecessary treatment add-ons. Our findings show experts dissatisfaction with the regulations of donor-eggs concerning reimbursement and registries in both countries.

Conclusions The adequacy of ART to solve age-related infertility should be confronted with alternative approaches, with emphasis on the distribution of accurate information. The magnitude of ART markets, particularly the use of donor-eggs, should raise the need for additional societal debate and the reform of regulations. The impact factors analysis leads us to question the current regulatory framework, which could be improved by nominating a non-governmental statutory central regulatory agency in Israel and by reforming the Spanish agency.

Keywords Assisted Reproductive Technology (ART) · In-Vitro Fertilization (IVF) · Regulatory Assessment · Delphi · Spain · Israel

Introduction

Assisted reproductive technologies (ARTs) 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 [24, 38]. 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 [1, 3, 81] and are fueled by environmental factors and the rising age of parenthood [13, 42, 44, 59, 80].

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 [47, 79]. The regulatory approach adopted by governments needs to cope with a constantly changing technical frontier and a

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certain level of uncertainty concerning the risks and benefits of ART, as is also the case with other emerging technologies [29].

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 among the most active users of ART [24, 38, 76]. Moreover, in both countries, policymakers have expressed fewer serious ethical and moral restrictions towards this field in comparison with other western countries [17, 83], 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 [39, 40]. It also builds upon the existing literature that has engaged in comparative analyses of ART regulations in the USA, Canada, the UK, and other European countries [17, 43, 63, 69, 70].

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 [60, 84]. This process allows experts to reach consensus or to suggest various alternative solutions which may be used for challenging future uncertainties [61, 64]. 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 [51, 74].

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.

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.

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.

Factors influencing regulation

The four main potential public interests in regulation proposed by Johnson and Petersen [45] 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" ([45], p. 717). Finally, sociopolitical interest refers to societal values commonly reflect increasing tolerance and permissiveness towards ART [44, 68]. Nevertheless, regulators should recognize values and beliefs and participate in the process of social change [35], to reduce fear, anger and adverse public debate [34, 45].

Empirical context

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 [17, 48]. Both countries can be characterized as "early adopters" [73] 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

Table 1 Regulatory dimensions

		References
1. Institutional settings		
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., UK, 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., USA).	[20, 63]
Regulatory approaches	- Legislation (most European countries)/voluntary guidelines (Japan, India, and the USA). - Pure-market approach (individual choice)/value-influenced approach (cultural factors)/value--based approach (society's values and ethical interest).	[45, 70]
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.	[27, 44, 70]
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.	[27, 71, 81]
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.	[4, 46, 67]
Gestational surrogacy	- Often banned or subject to strict approvals and limitations on monetary compensations. - Risk of uncontrolled development of international markets.	[9, 78]
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.	[7, 23, 32]
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.	[13, 42, 53, 59]
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.	[17, 20]
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.	[15, 27]

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

Table 2 Public interests influencing regulation

		References
1. Health interest		
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.	[17]
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.	[52, 53, 59]
Reduction of disabilities and severe genetic conditions	- Using PGD to avoid the birth of children with severe genetic conditions.	[22, 45]
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.	[25, 26]
Consanguineous marriage and reproductive risk	- Limiting to the number of donations from each donor. - Elaborating donor registries.	[45, 81]
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.	[71]
2. Economic interest		
Availability of public resources and procedures to set priorities	- Defining the ART provision and funding by public healthcare.	[19]
Reduction of future public health expenditure	- Preventing infertility. - Controlling adverse consequences of ART treatments, both related to children and to patients. - Using PGD to avoid the birth of children with severe genetic conditions.	[2, 22, 25, 65]
Gains of efficiency	- Addressing market failures, such as asymmetric information regarding outcomes, risks and costs. - Protecting the public from cartels and monopolies.	[45]
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.	[45, 67, 70]
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.	[4, 34]
Access to parents' identity	- Revealing a donor's identity may be important for children's autonomy and psychology.	[71]
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.	[5, 69]
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.	[35, 45]
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.	[16, 68, 72, 85]
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.	[36] [30]
Perception of the public health system and social responsibility	- Different concepts of justice and equity.	[45]

Table 2 (continued)

		References
Fertility rates	- Diverse attitudes towards markets and regulation in general lead to distinct ART regulations. - 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.	[8]

for healthcare management [6]. 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 [41]. 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 [16]. 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 [75, 76]). It also makes Spain among the highest in Europe in relative terms [24]. Finally, IVF births as a share of total births climbed to 8% in 2016, among the highest in the world [24].

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 [83]. 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 [9]. 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 [38].

Current regulations

Based on a review of regulatory documents and protocols/guidelines[1] 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 "Regulatory dimensions" section.

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 [12]. 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 [48, 82].

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,

[1] 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.

and also an important destination for reproductive tourism [5, 24, 76]. 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 [33, 62]. 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 [9].

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 [77, 83]. 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, 1513 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 [76]. 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.

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.

Method

The experts' selection and the development of a questionnaire are key issues in Delphi analysis [74]. 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 [54]. 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 [, 31]. 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.

A set of 27 in-depth semi-structured personal interviews lasting 1 h 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) [51]. 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 [50] and draw different scenarios [64]. Only one expert did not participate in the second round.

The statistical analysis was complemented with qualitative insights gathered through personal interviews and open

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. •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.	• 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 €.
• 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

Table 3 (continued)

Category	Israel	Spain
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 2450 € 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.
Donor 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 [76], Israel Ministry of Health, Boada et al. [12] and personal interviews

comments from both Delphi rounds, which were essential in shaping the analysis and explain the experts' consensus and dissensus.

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 the "Factors influencing regulation" section.

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.

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

Professional activity	Israel (18)		Spain (18)	
Doctors and health department 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)

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.

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

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.

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."

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

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.

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."

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 [76]. Moreover, in Israel, IVF cycles for this age group count for more than 40%, although with a much lower percentage using donor-egg [48]. 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 [16, 55, 57]. 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 [8, 10].

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 [18, 76]. However, as stated by some Spanish experts and as discussed by Bergmann [5], 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 [24], 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 [76].

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 [57], 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 [14] lead patients of advanced age to repeat many cycles using their own eggs with a priori low prospects [48], 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 [62]. 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 [80], and the potential of family-based exome and germlines sequencing among other methods [49, 66].

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 gray-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 [28, 37]. 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 [21].

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.

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" [56, 57]. 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" ([77], 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" ([67], 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 [11, 29], 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.

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