Title

Benefits, Challenges and Ethical Principles Associated with Implementing Non-invasive Prenatal Testing: A Delphi Study

Authors

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Running Title

Implementing Non-invasive Prenatal Testing

Abstract (249 words)

Background: Non-invasive prenatal testing is a recent technology that provides some genetic information about the fetus through the analysis of cell-free fetal DNA circulating in maternal blood. This study aimed to identify the benefits, challenges and guiding ethical principles most relevant to the clinical integration of non-invasive prenatal testing in Canada, according to experts throughout the country.

Methods: We conducted a 3-round Delphi study with Canadian experts of contemporary discussions about the ethical and societal implications of prenatal testing and/or genomic technologies. In Round 1, we asked participants (N=61; participation=20.2%) to identify clinical benefits and challenges related to the implementation of non-invasive prenatal testing in Canada, and ethical principles they think should guide it. In Round 2, we asked them (N=58; retention=95.1%) to select the most important elements stated by their peers. In Round 3, participants (N=49; retention=84.5%; overall retention=80.3%) were informed of the aggregated results from round 2, and invited to revise or confirm their selection.

Results: This paper presents and discusses three lists of benefits (N=10), challenges (N=27), and ethical principles (N=16) identified and prioritized by Canadian experts as most relevant to the implementation of non-invasive prenatal testing in Canada.

Interpretation: While pointing to a large diversity of potential issues, Canadian experts agreed on two sets of requirements for a responsible implementation of non-invasive prenatal testing in Canada: ethical requirements to actively promote free and informed decision-making on the part of prospective parents; and societal requirements to protect and promote the rights and interests of vulnerable individuals.

Keywords: Non-invasive prenatal testing, Delphi study, ethics, reproductive autonomy, decision-making, experts, knowledge translation, responsible innovation, Canada.

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Introduction

Non-invasive prenatal testing (NIPT) allows genetic testing through the analysis of cell-free fetal DNA (cffDNA) circulating in maternal blood. Although not as accurate as diagnostic tests such as amniocentesis or chorionic villus sampling, non-invasive prenatal testing may provide important benefits for pregnant women and their families. In contrast with invasive methods, it carries no risk of miscarriage. Non-invasive prenatal testing can also be performed early in the pregnancy (week 10-11) and has better detection rates than current first tier screening methods. The test is thus being gradually implemented worldwide. It is currently available in over 60 countries,[1] commercially in most, and covered by public funding in some. To date, in Canada, the provinces of Ontario and British Columbia offer public funding for non-invasive prenatal testing, but only under specific conditions.[2,3] More recently, the Quebec Ministry of Health announced that it will cover its use for high-risk pregnancies.[4]

Scholars and advocacy groups have expressed concerns regarding the potential consequences of 'routinizing' non-invasive prenatal testing.[5,6] These concerns include an erosion of free and informed consent, as well as the possibility of increasing termination rates, leading to decreased prevalence of certain genetic conditions, which may lead to a decrease in medical and social support for people and families living with these conditions.[7-10] It is therefore important to empirically assess the ethical and societal acceptability of non-invasive prenatal testing's clinical implementation and coverage through public funding, to ascertain that they reflect the interests, needs and values of Canadians.[11] Such decisions should be based on robust evidence regarding cost-effectiveness[12], and on the views and preferences of stakeholders.[13] In addition, we argue, these decisions should be informed by the evolving perspectives of Canadian experts on ethical and societal issues related to prenatal testing and/or genomic technologies. This study aimed to identify the most important benefits, challenges and guiding ethical principles regarding the clinical integration of non-invasive prenatal testing in Canada, according to such experts.

Methods

The Ethical Delphi technique, an "approach for characterizing ethical issues raised by the use of novel biotechnologies", was ideally suited to the aim of this study.[14] The classical Delphi method consists in surveying a panel of experts on a given topic, providing the panel with aggregate results, and obtaining feedback on the results in subsequent rounds. It promotes an honest, evolving and constructive exchange between people from diverse backgrounds aiming to identify areas of agreement and disagreement regarding emerging areas of knowledge.[15,16] It is a semi-anonymous method in which research participants are known to investigators but not to one another. Preserving such anonymity provides the respondents with the freedom to change their opinion from one round to the next, rather than defending a locked-in position with their name attached to it.[17] We conducted a 3-round Ethical Delphi study with participants with a diversity of experience with, knowledge of, and perspectives on the ethical and societal aspects of prenatal testing and/or genomic technologies.

Recruitment of the expert panel

We identified as potential participants individuals who had been actively involved in previous scholarly (e.g., academic literature) and/or public (e.g., newspaper articles) discussions on the ethical and societal aspects of prenatal testing and/or genomic technologies, and relevant professional or advocacy activities in Canada for at least 3 years. Individuals from four groups were recruited: healthcare professionals (N=17), researchers in social sciences and humanities (N=17), patient/disability rights advocates (N=17), and cultural/religious community advocates (N=10). Before completing round 1, participants were asked to confirm that they indeed identified as belonging to one of the four groups, and to specify their professional/academic or advocacy expertise (Table 1). We aimed for 10-15 respondents per group,[17,18] trying to ensure a >70% response rate in each round to minimize selective participant retention bias.[19,20] Special efforts were made during recruitment to account for language distribution, gender ratio, and geographic representation. A total number of 302 potential participants were thus gradually invited by email to this non-remunerated study, 61 of whom completed round 1 (initial participation rate: 20.2%).

Questionnaires and analysis

In round 1 (May-August 2015), research participants were asked to provide demographic and other relevant information about themselves. Using open-ended questions, we also invited them to state, in their own words, the most important "clinical benefits", "ethical, legal, and social issues and concerns", and "moral principles, social norms and values" related to the implementation of non-invasive prenatal testing in Canada. We formulated these questions as broadly as possible to avoid orienting participants' responses from the outset. For the same reason, we deliberately avoided importing concerns from the existing literature at any round of this study. Upon completion of round 1, Birko and Dupras independently assessed participants' responses, and clustered qualitative data using NVivo 10 (QSR International).

Following the process outlined by Burnard (1991),[21] three lists of non-redundant benefits (N=10), challenges (N=27) and guiding ethical principles (N=16) relevant to the implementation of non-invasive prenatal testing in Canada, were obtained. The second round (January-April 2016) questionnaire was created based on the responses and exact terminology employed by research participants in round 1. Using multiple-choice questions, we asked participants to select the most important benefits, challenges and principles that had been formulated by their peers, according to a) their own opinion, and b) their estimation of public opinion. The third round (September-December 2016) consisted of an identical set of multiple-choice questions, complemented by a quantitative presentation of the aggregate responses from round 2. Informed by the panel's position, participants had the opportunity to revise or confirm their responses. The three rounds were piloted by Haidar and Lemoine for face and content validity.

Ethics approval

Fonds du Québec pour la recherche – Santé et Culture provided funding for this project (FQRSC, #2014-NP-175854). We obtained ethics approval from the University of Montréal CÉRES (#14-104-CERES-D) prior to each round.

[ADD TABLE 1 HERE: PANEL COMPOSITION]

[ADD TABLE 2 HERE: INFORMATION ABOUT PARTICIPANTS]

Results

Of the 61 experts who completed round 1, 95.1% completed round 2 (N=58/61), of whom 84.5% completed round 3 (N=49/58). The resulting overall retention rate is 80.3% (N=49/61), with rates well over the 70% per round usually recommended for Delphi studies.[22] Among participants who completed the three rounds, 30.6% were healthcare professionals (N=15/49), 28.6% were researchers in social sciences and humanities (N=14/49), 28.6% were patient/disability rights advocates (N=14/49), and 12.2% were cultural/religious communities advocates (N=6/49) (Table 1). Our initial panel was highly heterogeneous in terms of participants' opinion about the "overall acceptability" of non-invasive prenatal testing in Canada, inquired using a Likert scale (1-7), with 55.1% (N=35/61) perceiving the test as *mostly acceptable* (1, 2 or 3), and 28.6% (N=17/61) viewing it as *mostly unacceptable* (5, 6 or 7). Such diversity was important given our objective of characterizing as many different views and concerns as possible. Table 3 presents the final lists of prioritized benefits, challenges and principles, as ranked by the panel following round 3.

[ADD TABLE 3ABC HERE: BENEFITS, CHALLENGES AND PRINCIPLES]

Interpretation

Summary

This paper reports the benefits and challenges related to the implementation of non-invasive prenatal testing in Canada, and the ethical principles that should guide it, according to local experts of ethical and societal issues in prenatal testing and genomic technologies. Throughout the three rounds, we paid special attention to reporting the exact terminology employed by research participants when stating benefits, challenges and principles. Our study thus has the advantage of offering a detailed landscape of the vocabulary used in practice by experts from diverse epistemological standpoints. Although many participants assigned value to non-invasive prenatal testing because of its 'increased accuracy', probably in contrast to current first tier screening methods, the panel largely agreed that the test's most salient benefits arise when comparing non-invasive prenatal testing to current second tier diagnostic methods ('no risk of miscarriage', 'non-invasiveness' and 'results available earlier in the pregnancy'). Our study thus confirms the main clinical benefits of non-invasive prenatal testing usually expected and discussed in the literature (safer, easier, earlier).[11] The panel expected the public to agree with the high ranking of these benefits, but believed Canadians could also be attracted by the idea that the new test 'provides more information potentially useful for decision-making' (supp. file). After carefully analyzing challenges and principles, we argue that our study points to two sets of requirements that should be prioritized according to Canadian experts: ethical requirements to actively promote free and informed decision-making for prospective parents; and societal requirements to protect and promote the rights and interests of vulnerable individuals.

Actively promoting free and informed decision-making

Participants unambiguously stressed how challenging offering ‘adequate counseling to patients’ can be, and yet largely agreed on the high importance of ‘informed decision-making’ in the context of prenatal care. Our findings thus resonate with the literature expressing concerns about the potential impact on informed decision-making of implementing non-invasive prenatal testing as “just another blood test”[23-26] and advocating the active promotion of women’s reproductive autonomy.[27-30] In addition to protecting ‘free choice’, participants in our study underscored the need to ensure the appropriate conditions for ‘evidence-based decision-making’. In this respect, they highlighted the difficulty of ensuring the ‘adequate education of health professionals’ about cutting-edge prenatal testing technologies and their potential ethical and societal implications.

Interestingly, the term ‘autonomy’ itself did not rank very high in the final list of principles. This concept may have been perceived as too vague by most participants, and/or not best reflecting what is truly at stake with the arrival of non-invasive prenatal testing in Canada. The term ‘consent’ also ranked surprisingly low on the list of challenges, suggesting that while Canadian experts value informed choice, they may believe that procedural modalities of signed consent forms are insufficient to adequately promote it.[31] In the context of non-invasive prenatal testing, promoting reproductive autonomy and protecting consent by prospective parents may instead require enhanced training of healthcare professionals regarding how to best communicate new testing options to patients, and the importance of understanding individual patients’ preferences. Preventing increased ‘pressure to test’ and ‘pressure to terminate’ – anticipated consequences of implementing non-invasive prenatal testing in routine prenatal care – is particularly crucial, given our participants’ estimation of free choice ranking first according to Canadians (supp. file). In the literature, such concerns have consistently been formulated by disability rights advocates, who fear that the emergence of new medical and social norms in prenatal testing may impose coercive pressures on pregnant women to test and terminate affected pregnancies masked as “responsible motherhood”, thus impeding the voluntary nature of their individual choices.[8,32-36]

Some empirical studies have shown that health care professionals tend to be in favor of testing and terminating affected pregnancies and may thus exercise subtle yet considerable influence on their patient’s decision-making process and final choice.[34,37] At the same time, some patients may expect clear recommendations from their health care provider, deliberately and admittedly intending to follow them.[9] To address the imperative of protecting free choice through the provision of relevant, adequate and sufficient information,[38] different strategies exist, such as *non-directive counseling* (focused on the patient’s decisional authority) or *shared decision-making* (focused on open discussion of personal values and opinions).[39,40] These strategies can increase a person’s freedom of choice by improving their understanding of the available options.[41-43]

Protecting and promoting the rights and interests of vulnerable individuals

Over half the participants feared that the implementation of non-invasive prenatal testing may lead to increased ‘discrimination against disabled individuals’. Many also shared concerns over ‘eugenics’, and a ‘potential decrease in social support for disabled individuals’ in the future. They estimated that the threat of eugenics ranks even higher in public opinion (second in the list of challenges; supp. file). Perhaps in response to these challenges, the principle of ‘respect for human dignity’ was perceived by the panel as very important for guiding the implementation of non-invasive prenatal testing in Canada. Many participants also underscored the need to continuously promote ‘respect for diversity’, and ‘solidarity with individuals living with the tested conditions'. These principles point to the societal imperative of being actively committed to the welfare of vulnerable groups. Disability scholarship literature has been useful in highlighting areas of needed improvement in this regard.[44-46]

While the 'cost of implementing' non-invasive prenatal testing did not rank high, most stressed the importance of ensuring 'equitable access' to the test. Indeed, if it is available only to those who can afford it, already vulnerable individuals or populations could be unfairly disadvantaged by not being offered the same opportunity to manage risks such as: a) the risk of miscarriage associated with publicly covered invasive techniques (e.g., amniocentesis), and b) the perceived burden (e.g., psychological, financial) of raising a child with a severe genetic condition.[40,47] It is worth noting that the cost of implementing non-invasive prenatal testing was estimated to rank first as challenge in public opinion. It remains unclear, however, whether the public is expected to be concerned about the economic burden being imposed on prospective parents (private funding) or on the healthcare budget (public funding). Empirical studies will be helpful in determining the specific criteria (e.g., level of risk, conditions tested for, paid out of pocket or publicly covered) the Canadian public and stakeholders think satisfy the principle of equitable access.

Limitations

We experienced difficulty in recruiting advocates of cultural/religious community advocates who had previously expressed their views regarding prenatal testing and/or genomic technologies. A plausible reason is that few may have considered themselves sufficiently knowledgeable about non-invasive prenatal testing and competent to engage in this study. The resulting lower number of participants in this group, however, should not be perceived as impeding the scientific validity of the results. In fact, our objective was not to *compare* the views of diverse groups of experts and search for statistically significant associations, but rather to shed light on a diversity of perspectives regarding non-invasive prenatal testing. The specific composition of our panel of experts (Tables 1 and 2) and the associated limitations should be considered when interpreting the results and their meaning for Canadian policy.

Being a pregnant woman or an individual living with a condition tested by non-invasive prenatal testing was not considered sufficient conditions to be invited to participate in this Delphi study. Empirical studies with Canadian stakeholders (e.g., PEGASUS surveys with pregnant women and their partners) will be instrumental in guiding policy-making.[13] However, in this study, we did not consider such stakeholders as 'experts of ethical and societal discussions related to prenatal testing and/or genomic technologies'. As reported in Table 2, women participants nevertheless represented more than half of the panel in each round, with 44.9% of the final panel (N=22/49) having experienced prenatal testing in the past. Considerable numbers of participants also reported either knowing a child (N=42/49), having a child (N=12/49), or living themselves (N=4/49) with a disability.

Conclusions

In addition to the ethical and societal considerations discussed above, it is worth noting that some of the issues highlighted by smaller proportions of participants in this study are also informative and should be considered. This is especially important if we care to consider the voices of persons with specific vulnerabilities, who due to their unique experiences of exclusion, may be more aware of and sensitive to particular ethical and societal issues related, for instance, to potential 'decreases in social diversity' that may follow increases in 'selective pregnancy termination'. Potential 'conflicts of interest linked to the commercialization of' non-invasive prenatal testing is another example of challenge that should be addressed. Otherwise, in the long term, the rise of distrust by some individuals towards the medical community could further impede effective communication about prenatal testing options between healthcare professionals and some of their patients. Thus, interdisciplinary appraisals of such issues may also be instrumental to responsible policy-making related to the implementation of non-invasive prenatal testing in Canada.

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Table 1. Panel composition

	Nb. of participants		
	Round 1	**Round 2**	**Round 3**
Health care professionals	**17**	**16**	**15**
Gynecologists-Obstetricians	4	3	3
Genetic counselors	3	3	3
Neonatalogists	3	3	3
Medical geneticists	2	2	2
Midwife	1	1	1
Nurse	1	1	1
Pediatrician	1	1	1
Other	2	2	1
Social science and humanities researchers	**17**	**17**	**14**
History	4	4	4
Law	3	3	2
Bioethics	2	2	2
Sociology	1	1	1
Anthropology	1	1	0
Philosophy	1	1	0
Other	5	5	5
Patients/disability rights advocates[1]	**17**	**16**	**14**
Association promoting social values	6	6	6
Association specific to Down syndrome	4	4	4
Association specific to an other condition	2	1	0
Involved in more than one association	2	2	2
Not affiliated to any association	3	3	2
Cultural/religious community advocates	**10**	**9**	**6**
Muslims	3	3	2
Christians	2	2	2
Jews	2	2	1
First Nations	1	0	0
Other	2	2	1
TOTAL	**61**	**58**	**49**

[1] We chose not to report the name of associations some experts had mentioned being affiliated with to protect the privacy of participants.

Table 2. Information about participants

A. **Demographics**

B. **Potentially influencing factors**

			% of participants		
			Round 1	**Round 2**	**Round 3**
A	**Language**[1]	English	70.5	70.7	69.4
		French	26.2	25.9	26.5
	Sex	Female	55.7	56.9	57.1
		Male	44.3	43.1	42.9
	Age	20-39	16.4	17.2	18.4
		40-59	49.2	48.3	46.9
		60-79	32.8	32.8	34.7
		80-99	1.6	1.7	---
	Country of birth	Canada	68.9	67.2	69.4
	Residence[2]	Québec	39.3	39.6	38.8
		Ontario	26.2	25.9	26.5
		Alberta	9.8	10.3	8.2
		British Columbia	8.2	8.6	8.2
		Manitoba	6.6	5.2	6.1
		Nova Scotia	3.3	3.4	4.1
	Degree completed[3]	Doctoral	60.7	60.3	61.2
		Masters	14.8	15.5	18.4
		Bachelor	11.5	12.1	10.2
		College	11.5	10.3	10.2
B	Have a child living with a disability		23.0	22.4	24.5
	Know a child living with a disability		86.9	86.2	85.7
	Live with a disability		8.2	8.6	8.2
	Experienced prenatal screening		47.5	43.1	44.9
	Experienced prenatal diagnosis		18.0	17.2	16.3
	Disclosed a commercial interest		1.6	1.7	2.0

1. Participants speaking other languages all together counted for 4.1% at round 3.
2. Residents of other provinces or territories all together counted for 8.2% at round 3.
3. One participant had an other level of education but did not complete round 3.

Table 3. Most important benefits (A), challenges (B) and guiding ethical principles (C) related to the implementation of NIPT in Canada following round 3.

A

BENEFITS	% of participants	Δ% (R3-R2)
1. No risk of miscarriage	83.7	+13.0
2. Non-invasiveness	63.3	+1.2
3. Results available earlier in the pregnancy	53.1	+6.3
4. Requires only a blood draw	42.9	+5.0
5. Increased accuracy	30.6	+8.2
6. Enhances prospective parents' ability to prepare	24.5	-11.7
7. Decreases anxiety for prospective parents	16.3	-7.8
8. Provides more information potentially useful for decision-making	16.3	-25.1
9. Answers specific needs	10.2	-3.6
10. Potential for NIPT to expand conditions tested	4.1	-8.0

B

CHALLENGES	% of participants	Δ% (R3-R2)
1. Adequate counselling of patients	79.6	+19.3
2. Pressure to test	67.3	+10.4
3. Adequate education of health professionals	65.3	+10.1
4. Discrimination against disabled individuals	59.2	+10.9
5. Pressure to terminate	55.1	+10.3
6. Eugenics	46.9	+2.1
7. Potential decrease in social support for disabled individuals	44.9	+1.8
8. Routinization of prenatal testing	38.8	+0.9
9. Stigmatization of the parents of children living with the tested conditions	38.8	-0.9
10. Accuracy of the test	34.7	-1.5
11. Decrease in social diversity	34.7	+5.4
12. Adequate professional guidelines	32.7	-5.2
13. Consent	32.7	+1.7
14. Cost of implementing NIPT	32.7	-1.8
15. Selective pregnancy termination	32.7	-5.2
16. What conditions to test	30.6	+8.2
17. Increased number of terminated pregnancies	30.6	-0.4
18. Conflicts of interest linked to commercia-lization of NIPT	28.6	-2.4
19. Misperceptions of the reliability of NIPT	28.6	-11.1
20. Existence of adequate policies	28.6	-5.9
21. Respect of human rights	26.5	-4.5
22. NIPT access-related issues	24.5	-1.4
23. Increased anxiety for prospective parents	18.4	-7.5
24. Conflict with religious values	14.3	+2.2
25. Assigning responsibility to care for the child	8.2	-0.4
26. Utility of the test	8.2	-12.5
27. Confidentiality of the results	2.0	-13.5

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PRINCIPLES	% of participants	Δ% (R3-R2)
1. Informed decision-making	81.6	+2.3
2. Evidence-based decision-making	59.2	+8.9
3. Respect for human dignity	53.1	+2.3
4. Equitable access	51.0	+7.9
5. Free choice	51.0	-0.7
6. Fair resource allocation	46.9	+0.3
7. Respect for diversity	44.9	+1.8
8. Solidarity with individuals living with the tested conditions	44.9	-10.3
9. Human rights	40.8	+0.6
10. Equality between persons	38.8	+6
11. Non-maleficence (do not harm)	36.7	-6.4
12. Autonomy	30.6	-7.3
13. Protection of privacy	28.6	-5.9
14. Sanctity of life	28.6	+4.5
15. Inclusiveness	22.4	-6.9
16. Beneficence	18.4	-5.7

- Supplementary file -

Expert estimates of public opinion

Benefits (ranking)	% of participants (R3)	Δ% (R3-R2)
1. No risk of miscarriage	67.3	-5.1
2. Non-invasiveness	61.2	+7.8
3. Results available earlier in the pregnancy	61.2	+6
4. Provides more information potentially useful for decision-making	42.9	+1.5
5. Decreases anxiety for prospective parents	40.8	-5.8
6. Requires only a blood draw	32.7	-3.5
7. Enhances prospective parents' ability to prepare	24.5	-6.5
8. Increased accuracy of the test	24.5	+2.1
9. Potential for NIPT to expand conditions tested	6.1	-2.5
10. Answers specific needs	4.1	-11.4

Challenges (ranking)	% of participants (R3)	Δ% (R3-R2)
1. Cost of implementing NIPT	63.3	+4.7
2. Eugenics	53.1	-0.3
3. Conflict with religious values	49.0	-2.7
4. Pressure to terminate	46.9	+2.1
5. Discrimination against disabled individuals	42.9	-1.9
6. NIPT access-related issues	42.9	+10.1
7. Pressure to test	40.8	+4.6
8. Adequate counseling of patients	38.8	-9.5
9. Misperceptions of the reliability of NIPT	38.8	-2.6
10. Increased number of terminated pregnancies	36.7	+0.5
11. Accuracy of the test	34.7	-3.2
12. Confidentiality	32.7	+5.1
13. Consent	32.7	+12
14. What conditions to test	32.7	-7
15. Respect of human rights	32.7	-3.5
16. Selective termination of pregnancy	32.7	-19
17. Stigmatization of the parents of children living with the tested conditions	32.7	+6.8
18. Adequate education of health professionals	28.6	+9.6
19. Adequate professional guidelines	26.5	+5.8
20. Conflicts of interest linked to commercialization of NIPT	26.5	-2.8
21. Potential decrease in social support for disabled individuals	22.4	-13.8
22. Existence of adequate policies	22.4	0
23. Routinization of prenatal testing	22.4	-1.7
24. Increased anxiety for prospective parents	16.3	-16.5
25. Utility of the test	16.3	+6
26. Decrease in social diversity	14.3	+2.2
27. Assigning responsibility to care for the child	12.2	+1.9

Principles (ranking)	% of participants (R3)	Δ% (R3-R2)
1. Free choice	79.6	+8.9
2. Equitable access	63.3	+13.3
3. Informed decision-making	63.3	-2.2
4. Protection of privacy	63.3	-5.7
5. Fair resource allocation	53.1	+11.7
6. Autonomy	42.9	+8.4
7. Respect for human dignity	38.8	-4.3
8. Sanctity of life	38.8	-4.3
9. Human rights	38.8	-11.2
10. Evidence-based decision-making	34.7	+0.2
11. Non-maleficence (do not harm)	30.6	-14.2
12. Equality between persons	28.6	-7.6
13. Respect for diversity	20.4	-14.1
14. Inclusiveness	16.3	-2.7
15. Beneficence	14.3	-4.7
16. Solidarity with individuals living with the tested conditions	12.2	-8.5