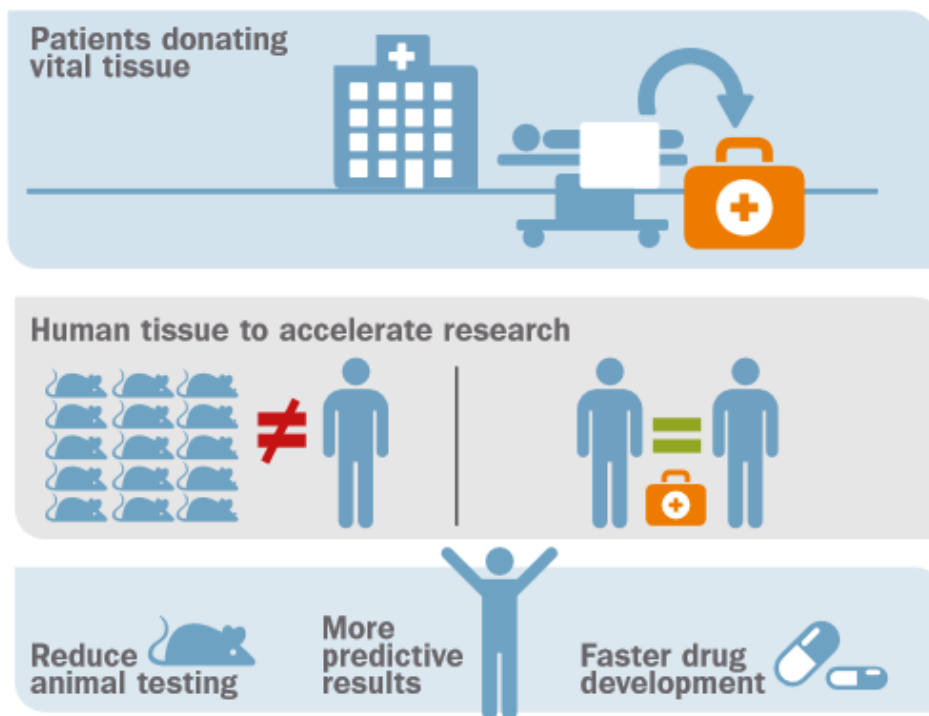


Ethical considerations in Dutch patients towards tissue donation for a human tissue supply chain to improve translational research



Summary

Introduction For years, animal testing has been the most frequently used method to perform a wide range of research in the Netherlands. However, due to a sub-optimal predictive value of these methods, many researchers have been advocating the use of human based models. Unfortunately, fresh, vital human tissue is difficult to access, and therefore still a lot of research is done using animal models. Consequently, results of pre-clinical studies into drugs and other products are difficult to translate to the human situation, which is one of the reasons why so many products fail in clinical studies. As a solution to the lack of accessibility of human tissue, TNO started project VitalTissue, which aims to develop an infrastructure between hospitals and research centres. Here, the idea is to bring surgical left-over tissue, obtained during operations inside the hospital, to research centres that are in need of fresh, vital tissue. This initiative aims to increase human tissue based research, thereby reducing animal testing and improving translational research. The latter could lead to more reliable research into drugs and other products, and eventually to a sooner and more efficient development process of these products. Before VitalTissue can be started, research into patients' (ethical) considerations is needed. Therefore, this study aims to contribute to a further development of a vital human tissue supply chain in the Netherlands, by examining (ethical) considerations among patients. The research question is as follows: what are patients' (ethical) considerations towards using surgical left-over tissue for research?

Methodology This was a mixed methods study, using semi-structured interviews and questionnaires. The research population was Dutch patients, which were defined as either being a patient currently, or being one in potential. As a result of this definition, all Dutch citizens were eligible as participant. In the end, nine interviews were conducted, lasting between 28 and 64 minutes. The interviews took place at the participant's home or at TNO Zeist. After analysis of interview data, a questionnaire was developed based on interview data, aimed at obtaining generalizable results on (ethical) considerations toward tissue donation for research. The questionnaire consisted of 10 questions and statements, which could be answered using a 1-7 Likert scale. Here, 1 represented 'I completely agree', 4 'Neither agree nor disagree' and 7 'I completely disagree'. To answer the research question, a conceptual model was developed from two previous studies. The model consisted of six concepts, including feelings aroused, knowledge of donation for research, motivations and perceived benefits, barriers and perceived dangers, justice and respect for autonomy. These concepts were used to derive six sub-questions that helped to answer the research question.

Results Overall, all nine interview participants were very positive about donating surgical left-over tissue to research. The most important benefits that were acknowledged were reducing animal testing and improving quality of translational research. Additionally, participants stated that if surgical left-over tissue would be thrown away anyway, it would be better to use it for research. As an important condition for success, participants reported transparency and openness is an essential concept. Furthermore, a number of concerns came up, the most important ones being a fear of misconduct by researchers and the danger of VitalTissue becoming a commercial, profit-driven tissue bank. Additionally, participants feared that operations inside the hospital would be influenced by the need for human tissue by researchers. Finally, participants distinguished between medical and non-medical research, and commercial and non-commercial research. In general, patients were more willing to donate tissue to medical, non-commercial research. In agreement with the interviews, the questionnaires showed a high willingness in 733 participants to donate surgical left-over tissue to research. However, many participants indicated to be reluctant to donate tissue to commercial organisations, like cosmetic and food companies. Strikingly, research into improved cosmetic products and food safety was approved more often. Furthermore, patients indicated to prefer signing informed consent, rather than an opt-out system, in which consent on use of left-over tissue is assumed unless otherwise indicated.

Discussion A high willingness was found in participants to donate surgical left-over tissue to research. However, a substantial part preferred medical research over non-medical commercial research, and some participants were reluctant to donate tissue to commercial companies. Additionally, transparency was a key concept among participants. It can be concluded that a widely accessible information supply is indispensable. Besides improved public support, it could also lead to understanding for the need of medical research as well as commercial research. Additionally, it could take away concerns about privacy and misconduct, as well as other existing concerns. Furthermore, sufficient monitoring is important for patients, as it provides assurance on ethical handling of tissue by researchers. Limitations of this study include lack of generalizability to subpopulations in the Netherlands with other cultural or religious backgrounds. Additionally, the study population of the questionnaire might be prejudiced on the topic of tissue donation for research, as they have the characteristic to be more than average willing to participate in research. Finally, only one researcher performed data-analysis, which might triggered error sensitivity. Future research should study the influence of cultural differences and religion on the topic of tissue donation for research. Furthermore, for VitalTissue is it essential to start focusing on the supply side of the market, and doing research into the willingness of hospitals and private clinics to cooperate in VitalTissue.

Results Questionnaire

This section provides the questionnaire results. As explained in the methods, the questionnaire was developed based on the interviews, and aimed to quantify the public support and ethical considerations towards a tissue supply chain.

5.9 Study population questionnaires

Table 2 provides descriptive information on 733 participants that completed the questionnaire. Originally, 742 questionnaires were submitted, but exclusion was performed on eight unfinished questionnaires and on one participant that was under the age of 16. The study population consisted of 270 (36.8%) men and 463 (63.1%) women. One participant filled in 'other' as gender possibility. Participants were between 16 and 84 years old. The mean age was 51, with a standard deviation (SD) of 16.3. Education level was subdivided in Dutch education categories, with secondary school and LBO representing the lower educated, MBO the middle educated, and HBO and WO the higher educated.

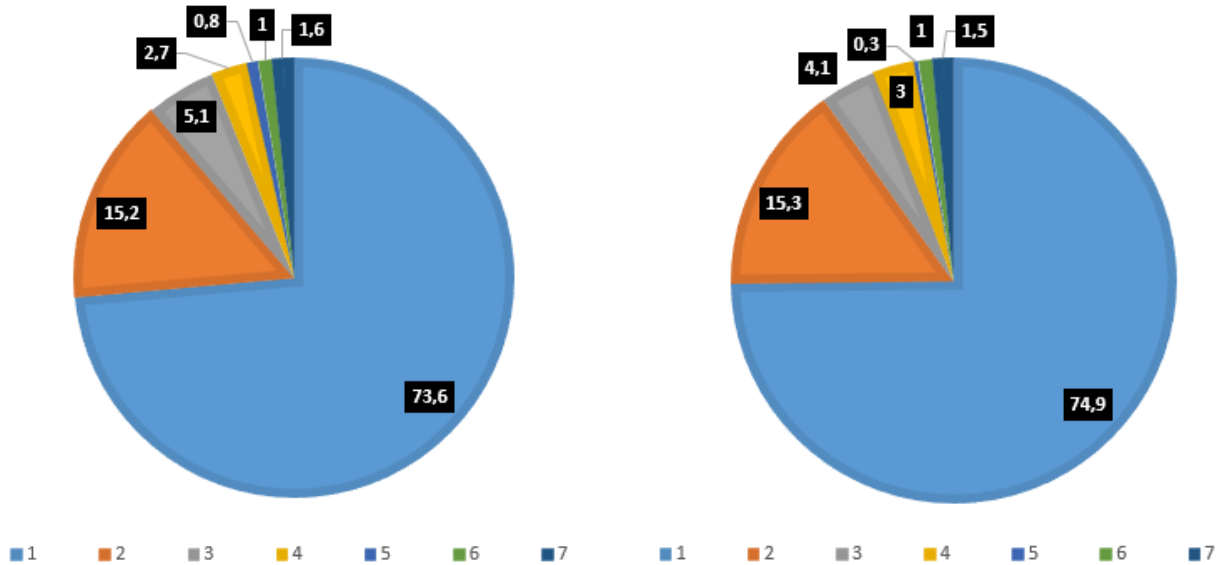
	Number	Percentage (%)
Gender		
men	269	36.7
women	463	63.2
other	1	0.1
Age		
<20	10	1.4
20-29	86	11.7
30-39	104	14.2
40-49	98	13.4
50-59	156	21.3
60-69	187	25.5
>70	92	12.6
Education level		
Secondary school	86	11.7
LBO	18	2.5
MBO	168	22.9
HBO	277	37.8
WO	174	23.7
Other	4	0,5
Unknown	6	0,8

Table 2. Descriptive information of participants that completed the questionnaire. Education is shown by the Dutch categories. Secondary school and LBO can be considered as lower educated, MBO as medium educated, HBO and WO as higher educated.

5.10 Feelings aroused: general willingness

Participants were generally strongly in favour of donating left-over tissue for research. The results of question 1-3, all applying to willingness to donate tissue, show respectively 73.6%, 74.9% and 77.5% of participants were strongly in favour of the statement. Moreover, another 15.2%, 15.3% and 13.0% respectively were in favour of statement 1-3 (score of 2). These data are visually represented in figure 5. The mean scores for the questions 1-3 were respectively 1.51, 1.47 and 1.45.

IT WOULD BE NO PROBLEM WHEN MY SURGICAL LEFT-OVER TISSUE WOULD BE USED FOR RESEARCH | **AM WILLING TO DONATE MY SURGICAL LEFT-OVER TISSUE FOR RESEARCH**



IF SURGICAL LEFT-OVER TISSUE WOULD BE DESTROYED ANYWAY, IT WOULD BE A WASTE NOT TO USE IT FOR RESEARCH

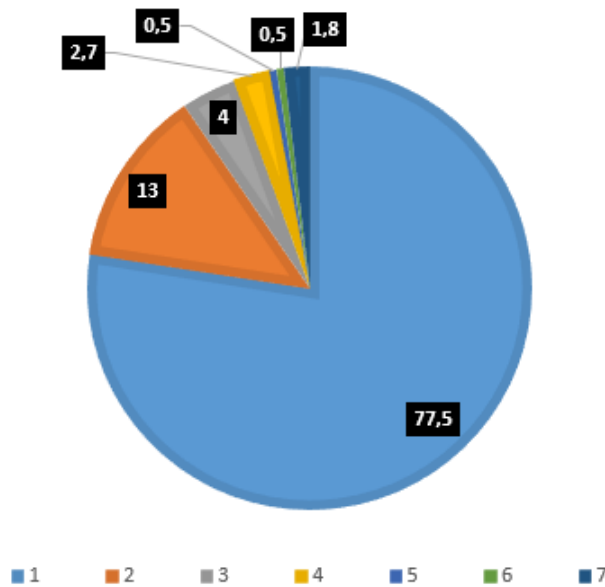


Figure 5. Questionnaire results from question 1-3. Numbers show the percentage of the study population. Top left: question 1; Top right: question 2; bottom: question 3. The numbers in the legend represent the Likert scores participants could choose. Implication of Likert scores: 1 'I completely agree'; 4 'neither agree, nor disagree'; 7 'I completely disagree'.

5.11 Justice: research purposes

5.11.1 Question 4

The results from question 4 showed many participants were in favour of donating tissue to research institutes and universities (table 3). The cumulative percentages (C%), obtained by adding the percentages of score 1 and 2, were 87.5% and 81.0% respectively. This indicates the percentage of participants (strongly) agreeing on donation for research to these organisations. Pharmaceutical companies and companies that produce medical instruments also scored high, with 77.2% and 77.8% (partly) agreeing to donate tissue (C% of score 1,2 and 3). However, these companies scored less positive than the research institutes and universities.

All non-medical companies and industries examined in question 4 scored considerably less than the medical companies and the academic or research institutes. The company that received most positive responses was the food industry, with 50.6% of participants indicating to be (partly) willing to donate tissue to this industry (C% of score 1,2 and 3). However, The agricultural and chemical industry had more divided results, with participants that agreed on donating and participant that did not agree on donating balancing each other approximately. Finally, considering cosmetic companies, more patients seemed to be unwilling than willing to donate tissue to this industry. Here, only 37.0% was (partly) willing to donate tissue.

Question 4: What kind of organisation would you allow to use your tissue for research?								
Industry/ Organisation	1	2	3	4	5	6	7	Mean score
Likert score								
Research institute	71.3	16.1 (87.5)	4.1 (91.6)	4.4 (96.0)	0.8 (96.8)	1.0 (97.8)	2.2 (100)	1.59
University	67.0	14.0 (81.0)	8.4 (89.5)	5.1 (94.6)	2.1 (96.7)	1.0 (97.6)	2.4 (100)	1.74
Pharmaceutical company	50.2	16.7 (66.9)	10.2 (77.2)	12.1 (89.2)	2.9 (92.1)	1.7 (93.8)	6.2 (100)	2.31
A company for medical instruments	51.8	16.5 (68.3)	9.4 (77.8)	10.1 (87.9)	3.5 (91.4)	2.6 (94.0)	6.0 (100)	2.29
Food company	28.8	11.3 (40.1)	10.6 (50.6)	16.9 (67.6)	8.3 (75.9)	7.2 (83.1)	16.9 (100)	3.54
Cosmetic company	21.3	7.6 (28.9)	8.2 (37.0)	15.1 (52.1)	10.4 (62.5)	8.7 (71.3)	28.7 (100)	4.27
Agricultural industry	24.3	8.6 (32.9)	9.7 (42.7)	16.2 (58.9)	8.5 (67.4)	10.2 (77.5)	22.5 (100)	3.96
Chemical industry	21.2	6.7 (27.9)	7.7 (35.7)	15.9 (51.5)	8.6 (60.1)	11.4 (71.5)	28.5 (100)	4.32
Every organisation that								3.84

Table 3. Questionnaire results from question 4. Numbers show the percentage of the study population. Between parenthesis, the C% (cumulative percentage) is shown. The darker blue column shows the mean score. Implication of Likert scores: 1 'I completely agree'; 4 'neither agree, nor disagree'; 7 'I completely disagree'.

5.11.2 Question 5

Considering research purposes, examined by question 5, participants reported a high willingness towards donating tissue for medical research and research aimed towards promoting, protecting and improving human health. For instance, 93.7% of participants indicated to be (strongly) willing to donate tissue for research into the workings of human diseases (C% of score 1 and 2). Furthermore, research aimed to promote, protect or improve human health scored relatively well, with 80.7% of participants indicating to be (partly) willing to donate tissue in this situation (C% score 1,2 and 3). Other research aims received less positive response, but still the majority of participants seemed to be willing to donate tissue. The only exception was research into less harmful tobacco products, which received a mean score of 4.66 with 41.3% of participants indicating to be strongly opposed to donating tissue for this kind of research (table 4).

Question 5: To what research purposes would you donate your tissue?								
Purpose	1	2	3	4	5	6	7	Mean score
Likert score								
Research into the workings of diseases inside the human body	81.5	12.1 (93.7)	2.8 (96.4)	0.4 (96.8)	0.4 (97.2)	0.4 (97.7)	2.3 (100)	1.37
Drug research	71.9	15.3 (87.2)	5.4 (92.6)	2.8 (95.3)	0.7 (96.0)	1.0 (97.0)	3.0 (100)	1.60
Research towards medical instrument	58.1	17.1 (75.2)	8.9 (84.1)	7.2 (91.4)	2.1 (93.5)	2.5 (96.0)	4.0 (100)	2.02
Research into safety of cosmetic product	26.1	9.8 (35.9)	13.3 (49.2)	17.6 (66.8)	7.5 (74.3)	7.3 (81.6)	18.4 (100)	3.66
Research into environment protection	40.8	15.1 (55.9)	11.5 (67.3)	13.5 (80.9)	5.4 (86.3)	3.8 (90.1)	9.9 (100)	2.79
Research into less harmful tobacco products	22.3	4.9 (27.2)	4.8 (32.0)	11.7 (43.7)	6.5 (50.1)	8.6 (58.7)	41.3 (100)	4.66
Forensic research	46.9	14.2 (61.1)	7.5 (68.6)	15.9 (84.5)	3.9 (88.4)	2.9 (91.4)	8.6 (100)	2.59
Research into food safety	41.6	15.3 (56.9)	13.2 (70.2)	13.9 (84.1)	5.0 (89.1)	2.9 (92.1)	7.9 (100)	2.66
Education for (medical) students	50.7	16.4 (67.1)	11.5 (78.6)	9.7 (88.3)	4.2 (92.5)	2.8 (95.3)	4.7 (100)	2.28
Every research aiming to promote, protect or improve human health	55.0	16.9 (71.8)	8.8 (80.7)	10.2 (90.9)	3.3 (94.2)	1.1 (95.3)	4.7 (100)	2.12
Every research in which animal tests could be	51.3	12.8 (64.2)	10.5 (74.6)	13.7 (88.3)	2.8 (91.1)	2.4 (93.4)	6.6 (100)	2.37

Table 4. Questionnaire results of question 5. Numbers show the percentage of the study population. Between parentheses, the C% (cumulative percentage) is shown. The darker blue column shows the mean score. Implication of Likert scores: 1 'I completely agree'; 4 'neither agree, nor disagree'; 7 'I completely disagree'.

5.11.3 Additional concerns

Question 5 enabled participants to indicate additional concerns involving research organisations using tissue for various purposes. Most concerns that came up were mentioned as well in the interviews. Firstly, participants reported medical or non-commercial research should be prioritized over non-medical and commercial research. This implied that only when abundant tissue is available, the latter should be able to apply for human tissue. Other participants indicated not to be willing to donate tissue to commercial companies at all. A frequently used argument for this was that financial interests and research with human tissue were not compatible. A second issue was the use of human tissue for research into tobacco products, which participants often firmly refused. This also applied to research into cosmetics, although fewer participants were opposed to this. A third frequently mentioned issue was transparency on tissue use for research. Many participants reported that as long as they are aware and are enabled to give permission, their tissue could be used for research. In summary, participants had difficulties with profit-driven companies, and preferred donating their tissue to research aimed at improving health care and reducing animal testing.

5.11.4 Question 6 and 7.

The results of questions 6 and 7, shown in figure 6, confirmed that a majority of participants preferred a checklist option, enabling them to opt-out specific organisations or purposes. In accordance, a considerable part of participants expressed to be worried about what would be done with their tissue. These results, together with the results from question 5 and 6, all show a need among participants to keep in control of their tissue once it has been donated.

Questionnaire results of question 6,7 and 9

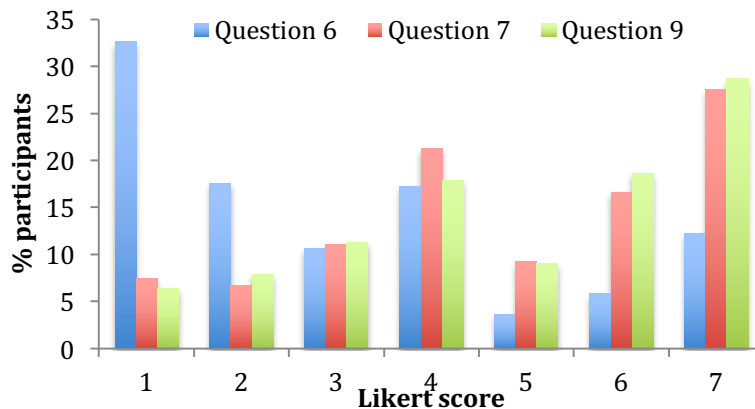


Figure 6. Questionnaire results from question 6, 7 and 9. The figure shows what scores participants chose most frequently. Question 6: I would like to be able to explicitly indicate for what purposes my tissue can be used; Question 7: I would be worried about what would be done with my tissue; Question 9: I would be worried about privacy, even when assurance is provided that data are confidentially and anonymously processed. Implication of Likert scores: 1 'I completely agree'; 4 'neither agree, nor disagree'; 7 'I completely disagree'.

5.12 Barriers and perceived dangers: Privacy

Question 8 and 9 focused on privacy and on personal data use for research purposes. Firstly, the results of question 8 are shown in table 5. The response to this question shows that a large majority of participants did not have a problem with using personal information for research, although it partly depended on the kind of information. Overall, participants did not have trouble with use of personal information for research, considering the large amount of scores between 1 and 4. For example, the lowest C% at score 3 was 82,9% for health status, indicating this portion of participants (partly) agreed this information could be used for research. In accordance with question 8, the results of question 9 (figure 5) show a considerable part of participants would not worry about privacy. However, responses on this question were divided. Although the majority indicated not to worry about privacy, a substantial minority (partly) agreed on the statement. Thus, although many participants indicated not having problems with privacy, it remains a topic of interest.

Research could in a confidential and anonymous way use personal information like my:								
Type of information	1	2	3	4	5	6	7	Mean Score
Likert score								
Age	73.3	14.3 (87.6)	3.0 (90.6)	5.9 (96.5)	1.1 (97.5)	0.5 (98.1)	1.9 (100)	1.56
Gender	73.0	14.9 (87.8)	2.7 (90.6)	5.5 (96.0)	1.1 (97.1)	0.8 (98.0)	2.0 (100)	1.58
Health status	62.6	15.2 (77.7)	5.2 (82.9)	9.3 (92.2)	2.6 (94.8)	2.2 (97.0)	3.0 (100)	1.93
Drug use	63.7	14.1 (77.8)	5.2 (83.0)	9.6 (92.6)	2.6 (95.2)	1.5 (96.7)	3.3 (100)	1.91

Table 5. Results of question 8. Numbers show the percentage of the study population. Between parenthesis, the C% (cumulative percentage) is shown. The darker blue column shows the mean score with the SD (standard deviation). Implication of Likert scores: 1 'I completely agree'; 4 'neither agree, nor disagree'; 7 'I completely disagree'.

5.13 Respect for autonomy: opt-in versus opt-out

The final question on opt-out versus opt-in showed a minor preference towards the latter. 54.4% indicated that tissue could not be used without a signed informed consent form, while 45.6 preferred a system in which consent on use for research is assumed, unless otherwise indicated. Figure 7 visually shows the results of the question on opt-out versus opt-in.

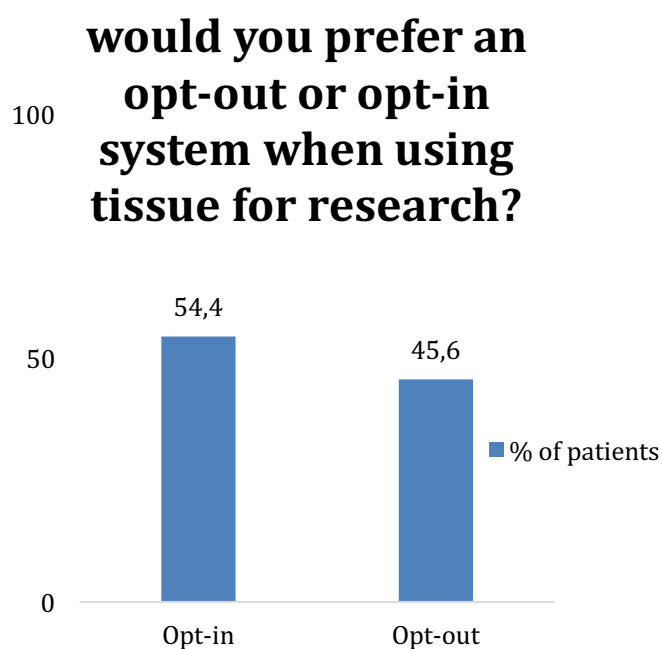


Figure 7. Results of question 10. Numbers show the percentage of the study population.

Resultaten vrije opmerkingen enquête

Misbruik

Angst dat meer weefsel wordt weggehaald dan nodig/akkoordje	10	
Geen informatie naar de verzekeringsmaatschappij	3	
Angst voor misbruik door bedrijven	2	
Angst illegale praktijken		1
Zorgen naleving privacy beleid door industrie		1
Geen verkwisting van restmateriaal door bedrijven/organisaties	1	
Niet betalen voor weefsel, handel in weefsel		1

Opt-in / opt-out

Opt-out onder voorbehoud (bv wanneer voldaan aan bep. veiligheidseisen)		9
Opt-out toegestaan, mits voldoende informatieverschaffing naar patiënt	2	
Opt-in		1

Belangrijke motivaties

Drieproeven moeten stoppen		9
Het zou zonde zijn restweefsel niet te gebruiken		7

Openheid/communicatie naar patiënt

Ik wil weten waar mijn weefsel voor wordt gebruikt (doeleinde, industrie)	8	
Patiënt informeren dat weefsel gebruikt kan worden voor onderzoek		5
Terugkoppeling onderzoeksresultaten naar donateurs		4
Hoe weet ik dat mijn DNA veilig is?	4	
Is er een einddatum aan het gebruik van weefsel?	3	
Wie maakt er gebruik van weefsel? (ook AIVD?)		2
Transparantie	1	
Is onderzoek met DNA niet per definitie niet-anoniem		1
Interesse in vervolg VitalTissue		1
Moeten mensen hier invloed in hebben? In geding komen onderzoek		1
Wat is chemisch? (chemische industrie)		1
Is er sprake van vergoeding?	1	

Medisch onderzoek / commercialiteit / niet-medisch onderzoek

Moeite met bedrijven vanwege het winstoogmerk	8	
Algemeen nut moet voorop staan (in tegenstelling tot bv winst)	6	
Bedrijven zouden een vergoeding moeten betalen	4	
Er mag alléén medisch onderzoek gedaan worden met mijn weefsel		2
Moeite met commerciële doelen/onderzoek		2
Medisch onderzoek moet voorrang krijgen	2	
Alle doeleinden zijn toegestaan		1
Duurzaamheid voorop		1

Rol privacy, anonimiteit, gegevensverstrekking

Sommige persoonlijke gegevens mogen worden meegestuurd, mits anoniem		7
Privacy(waarborging) essentieel onderdeel	7	
Privacy waarborging is moeilijk te realiseren	3	
Persoonlijke gegevens in een afgescheiden/afgesloten databank	1	
Databank onwenselijk		1
Er moeten grenzen komen/specifieke regels bij DNA sequensen	1	
Geen langdurige opslag, na verbruik vernietigen	1	
<u>Ethiek/ Ethische omgang met weefsel / regelgeving</u>		
Zorgvuldige omgang voorop	3	
Geen foetaal/embryonaal weefsel gebruiken		2
Wettelijk vastleggen regels en afspraken omtrent onderzoek met weefsel	2	
Afwijzing VitalTissue vanwege geloof	1	
<u>Interesse als afnemer</u>		
Werkzaam in preklinisch onderzoek, interesse weefselafname		3
<u>Patiënten delen mee in winst</u>		
Besparing terugvloeien naar patiënt	3	
Gevolg van VitalTissue: minder dure medicijnen		1
<u>Kritiek op vragenlijst</u>		
Voor toestemming hangt veel af van de situatie, vragen te zwart wit		2
Kritiek/onduidelijkheid optie neutraal		1
<u>Overheid betrekken</u>		
Rol voor de overheid in VitalTissue	2	
Uitbreiding van het donorcodicil met VitalTissue	1	
Is er politieke steun?	1	