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Obtaining 'fresh' consent for genetic research with biological samples archived 10 years ago

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ABSTRACT

Objective: To obtain consent from breast cancer survivors to use residual tissue for a study on carriership of germ line mutations in the BRCA 1 and 2 genes. To investigate which consent regimen patients prefer for research with archived tissue.

Participants: One hundred and thirty-two patients surgically treated for breast cancer between 1995 and 1997 in the Netherlands Cancer Institute were mailed a consent form and a questionnaire.

Results: A consent form was obtained from 90%; 3% withheld consent for the use of archived tissue. A completed questionnaire was returned by 84%. 'One-time general consent' was considered to be the best procedure for consenting to research with stored tissue by 56%, 23% favoured the current 'opt-out' procedure; 21% did not know or had no preference.

Conclusion: Obtaining fresh consent for genetic research with stored tissue is possible at the cost of time and effort. Most patients give consent for research with residual tissue.

1. Introduction

Human tissue stored after clinical procedures is an exceedingly important resource for medical research.[1,2] Consent for use of stored tissue for research purposes can be obtained in a variety of ways, and there is on-going discussion about which procedure complies best with patients' wishes while also being feasible. Some argue that implied consent with the opportunity to opt-out is sufficient.[2–5] Others claim that explicit 'one-time *general*' (for all future research) consent should be asked.[6,7] An alternative is 'one-time *specific* consent' with opportunities to have more control over future uses of tissue.[8,9] Patients can also be asked for *fresh consent* at the start of research, a procedure of which thus far only Furness and Nicholson[10] have reported.

European national legal systems differ as to whether it is required to obtain fresh consent for the use of residual coded tissues in scientific research.[11] Genomic studies could have consequences for the individuals or families if data are released.[12–14] The recent 'Draft Guidelines for Human Biobanks and Genetic Research Databases' of the OECD[15] only apply to tissue banks established for research purposes, thereby missing the vast potential resource of stored residual tissue. Asking consent for the use of these collections in biobank research would mean re-contact and fresh consent.

In the Netherlands, anonimised samples obtained during medical treatment may, according to the Dutch Act on the Medical Treatment Contract,[11,16] be used in medical research if the patient has not objected to this 'secondary use'. Active consent for the use of such materials is not required and the

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law does not specify how patients should be informed about secondary use of tissue. The Dutch Federation of Medical Scientific Societies, together with patient groups and the Royal Dutch Medical Association, established a Code of Conduct for the use of residual tissue in research.[17] This self-regulation extends the scope of the 'opt-out' procedure to include the use of coded tissue. The need for a new law about the use of tissue for research is currently being considered. While some argue that explicit consent should be obtained,[18] others favour an opt-out procedure.[11] The present study aims to contribute to the debate about consent regimens by providing data on the practice of obtaining fresh consent for genetic research in a population of cancer patients. We also investigated patients' preferences for various consent regimens.

2. Methods

2.1. Research setting

This study was performed in the framework of a project addressing the prognosis of breast cancer in carriers of mutations in the breast cancer associated genes.[19,20] We identified a retrospective cohort of breast cancer patients for whom paraffin-embedded tissue blocks were available for DNA isolation and subsequent mutation analysis. To protect the privacy of patients, a special procedure was developed which double codes tissue, rendering the data anonymous at the level of the investigator. This procedure is explained in a separate paper.[19,21] For patients surgically treated before the Act on the Medical Treatment Contract came into effect (1995), tissue blocks could be used based on the Code of Good Conduct. For patients treated in the first years after 1995, it was unknown whether they were informed about research and had the opportunity to opt-out of research with their stored tissue.

The primary objective of the current study was to determine the extent to which members of this cohort were willing to give consent for the use of their stored tissue, and their attitudes towards being provided with the opportunity to give (or withhold) such consent. We also investigated women's' preferences for various consent procedures.

2.2. Patients

Using the tumour registry of the Netherlands Cancer Institute, we identified all patients in the hospital who were treated for operable breast cancer before the age of 50 years between 1995–1997 ($N = 132$) and were alive and disease-free in 2006.

2.3. Data collection procedures

All patients were sent a letter and an information leaflet about the research project, a consent form and a stamped return envelope. Patients were asked to return both the consent form and the questionnaire. One month after the letters had been mailed, non-respondents received a reminder with the same study materials. Patients who did not respond after the reminder were contacted by phone after one month.

The information leaflet explained the background and aims of the research. It was also explained that, although rare, 'incidental findings' with implications for the patient's health might emerge from the research. The consent form therefore asked for consent to use stored tissue for BRCA 1/2 testing and also whether the patient wished to be informed about incidental findings.

The questionnaire covered a range of topics, including attitudes towards having been given the choice about tissue use, opinions about the best procedure for informing patients and for requesting consent from patients, and attitudes towards genetic and commercial research, tissue storage and ownership of tissue.

The question about the various consent regimens was introduced by explaining that one-time general consent is a model in which the patient is informed and actively asked for written permission for all future research with archived tissue. Opt-out was described as the model in which the patient is not actively informed and not actively asked for consent; information about research with tissue is available in the general leaflet of the hospital and the patient can opt-out.

All respondents were asked to cooperate with a telephone interview. A selected number of questions from the written questionnaire were discussed in-depth during these interviews, with particular emphasis placed on the questions about consent regimens, how patients perceived the storage and use of tissue, and types of research for which patients wished to give consent. If the respondent agreed, the Interviews were tape recorded and subsequently transcribed. The study was approved by the hospital's institutional review board.

2.4. Statistical analysis

In the analysis, we compared the distribution of preferences for different consent regimen between subgroups according to patient's age, educational level and convictions of ownership of tissue using Pearson's χ^2. All tests for statistical significance were two-sided.

3. Results

3.1. Response rate and patient characteristics

Of the 132 patients approached by mail, 119 (90%) returned the consent form. Half (51%) were returned after the first letter, 30% were returned after a written reminder. One patient sent back all documents in an unopened envelope with the explicit message not to contact her. We called 17 patients by telephone, 12 of them (9% of all mailed women) returned the consent form. Before approaching these patients by telephone, we checked whether their medical charts indicated reasons not to contact them, 3 were not contacted and one had recently died. A further three patients could not be contacted by mail or telephone, one of them had died.

We obtained 114 questionnaires (86%), 111 (84%) of these could be used in analysis. We obtained consent for a telephone interview from 81 patients (68% of responding patients). General characteristics of the respondents are shown in Table 1. The median age of the responders at time of the study was 56 years. Fifty-seven percent of the respondents had advanced vocational or university education.

Table 1 – Characteristics of respondents.

	All respondents		Interviewed	
	(*N* = 111)	%	(*N* = 81)	%
Age (at time of study)				
>60 years	11	10	6	7
59–50 years	79	71	56	69
<49 years	21	19	19	24
Median age of responders (range)	56 years	38–62	55 years	38–62
Median age of non-responders (*n* = 13) (range)	55 years	43–62		
Educational level[a]				
Low	4	4	2	2
Intermediate	49	44	32	39
High	58	52	46	57
Educational level of non-responders (n = 13)				
Low	0	0		
Intermediate	4	30		
High	7	54		
Missing	2	15		
No. (%) with a professional occupation	75	68	58	72
No. (%) with a religious affiliation	47	42	32	39
No. (%) feeling healthy	89	80	63	78

a Low level education: primary school, lower vocational training or lower general training; intermediate level: intermediate vocational or intermediate/higher general; high level: higher vocational or university training.

3.2. Consent for use of stored tissue

Only 4 respondents (3.4%) withheld consent, 2 in response to the first mailing and two in response to the telephone reminder. One respondent, an insider in health care with a university degree, was convinced that all of her tissue would be used in research, leaving nothing for clinical use, if needed. Another respondent with a university degree did not want her tissue investigated for germ line mutations for fear that she would be informed about being a mutation carrier (despite the fact that the information leaflet explicitly indicated that this would not be done). The two other respondents who declined to give consent stated: 'The tissue has been there for such a long time. It is kept in trust, better leave it alone. I do not want new findings to come out; I don't want to make choices again.' Some consenters also expressed uncertainty or anxiety about the chance to be informed about an incidental finding. The majority of respondents who consented to the research (97%) however, wished to be informed about incidental findings.

The most common reasons for providing consent were not caring about what happened with their tissue and a desire to contribute to improving treatment for future patients. Consent was also provided because respondents thought that they would be informed about research findings, although they were informed that research findings would not be reported. Many (57%) thought that they had the right to be informed about research findings.

3.3. Preferences for consent regimens

One-time general consent was preferred by 56% of the respondents, 'opt-out' by 23%, 21% had no preference or did not know which regimen they preferred (Table 2). Older respondents (>50 years), those more highly educated, and those who did not consider themselves to be the owner of their stored tissue or DNA were more likely to favour the opt-out regimen, although these associations were not statistically significant (age [$\chi^2 = 8.0$; df. 6; $p = 0.23$], educational level [$\chi^2 = 4.2$; df. 6; $p = 0.64$] and conceptions of ownership [$\chi^2 = 3.9$; df. 3; $p = 0.26$]) (Table 3). A minority of respondents (23%) felt that it would be appropriate for a 'representative body' to make decisions about tissue use; as this would relieve patients of the necessity or responsibility of making a choice.

During the interviews, the potential drawbacks of the one-time general consent regimen versus the opt-out regimen were discussed with the 45 respondents who had indicated in the written questionnaire that they favoured one-time general consent. Potential barriers and problems discussed included time constraints, additional paperwork, asking consent from individuals who otherwise would not want to be confronted with such decisions and low response rates. After these discussions, 26 respondents (58%) still preferred one-time general consent but their preference for this regimen was based primarily on the desire to be informed; the opportunity of making a choice in itself was not critical to them. Some of them suggested an alternative model (to the Dutch context in which information about tissue is not provided actively): inform patients about storage and use of tissue actively and give the opportunity to read more about it in an information sheet so that they can contemplate to opt-out.

3.4. Obtaining fresh consent

We evaluated the model of fresh consent and more specific consent for future research. Although most respondents (92%) appreciated having had the choice, almost half of the respondents (49%) thought that asking consent for the

Table 2 – Patient preferences regarding consent regimen.

	All respondents		Interviewed	
	(*N* = 111)	%	(*N* = 81)	%
Type of consent regimen				
I think 'opt-out' is the appropriate consent regimen	26	23	22	27
I think 'one-time general consent' is appropriate	62	56	45	56
I have no opinion/do not know which regimen is best	23	21	14	17
More control over future research				
I gave permission for this research but not for other future research because I want to be able to give consent for future research	49	45	36	44
I think patients should be able to indicate in which kind of future research their tissue may or may not be used	73	61	52	64
I would appreciate to be able to indicate in advance whether my tissue could be used in commercial research	70	59	57	70
Timing of information. When should information about tissue use in research be given?				
I want information provided during the hospital stay	54	49	38	47
I want information provided after the hospital stay	49	44	35	43
I think it should be given at another moment	8	7	8	10
How should the written information be provided?				
In the general hospital leaflet	48	43	34	42
In a specific leaflet	58	52	43	53
No information should be provided	2	2	2	2
Information should be offered otherwise	3	3	2	2

research project was not really necessary. Approximately one-quarter of the respondents were aware that tissue had been stored and that this tissue could be used in medical research, so the request for consent came as a surprise to most: 'You still have my tissue?', or a comparable question was often brought forward during the interviews. A minority (30%) felt that the request stirred emotions because it remembered them of breast cancer.

Respondents (64%) trusted privacy regulations for research with tissue, 11% had doubts and 25% did not know. The trust was based upon the hospital and its physicians. Most respondents (70%) did not think it was necessary and appropriate to ask relatives to provide consent for tissue research after they themselves had died, 21% did, others did not know.

In the telephone interviews, we also discussed the drawbacks of repeated fresh consent for new research. After discussion of potential problems with the fresh consent model: the need to repeatedly contact people with difficult questions and with information that would remind them of their cancer experience, increased paperwork, difficulty in locating individuals and potentially high non-response rates, only half of those who initially favoured this model continued to do so.

Table 3 – Preferences regarding consent regimen by patient characteristics.

	Prefers 'opt-out' (*n* = 26) %	Prefers 'one-time general consent' (*n* = 62) %	No preference/do not know (*n* = 23) %
Educational level (χ^2 = 4; df. 6; p = 0.64)			
Low (*n* = 4; 4%)	25	50	25
Intermediate (*n* = 49; 44%)	18	63	19
High (*n* = 58; 52%)	28	50	22
Missing[2]			
Age (χ^2 = 8; df. 6; p = 0.23)			
>60 (*n* = 11; 10%)	36	36	27
59–50 (*n* = 79; 71%)	24	56	20
<49 (*n* = 21; 19%)	14	67	19
Ownership of tissue (χ^2 = 3.9; df. 3; p = 0.26)			
Feels she is still owner of the stored tissue (*n* = 58; 53%)	17	64	19
Feels she is no longer owner of the stored tissue (*n* = 51; 47%)	31	45	24
Missing[2]			

Many respondents (45%) indicated that they gave consent for the research project but that they would prefer to be informed about future other research projects with their tissue. Many (61%) were in favour of a procedure that would provide authorisation about types of future research with their tissue in advance (Table 2). Many (70% of interviewed) respondents would appreciate to be able to indicate in advance whether tissue could be used in commercial research. Genetic research was thought to be valuable and unproblematic but 'commercial research' was often rejected. Respondents approved of research with their tissue because it could help future patients; 'commercial research', in which profit would be made by using tissue, was seen to contradict the interests of the common good because the knowledge gained through research of the tissue would not become available to everyone.

4. Discussion

Our study is the first one reporting on a procedure to obtain fresh consent for research with tissue archived after surgery for cancer in the distant past. In this research we used and studied the fresh consent procedure, we obtained consent forms from 90% of patients. The large majority (97%) gave consent for genetic research with archived tissue, some after considerable effort. Studies in other settings reported similar consent rates.[5,10,22–27]

Most respondents (92%) appreciated being asked for consent but many (49%) thought it was not really necessary because they endorsed research on breast cancer. Fifty-six percent of respondents considered 'one-time general consent' to be the best procedure for consenting to research with stored tissue, while 23% favoured the current 'opt-out' procedure and 21% did not know or had no preference. However, during interviews more than half of the respondents who initially chose 'one-time consent', voiced the opinion that it was more important to be informed about tissue use than actually have the opportunity to give or withhold consent for research. Patients feel respected and valued by being asked for consent, considering the opportunity to actually give consent of secondary importance.[28]

Genetic research as such was not considered to be a problem by the respondents, as was also observed in other research settings.[29,30] Surgically resected tissue had no special emotional value for most respondents,[31,32] but they were keen to know what happens to their removed tissue.[33] Many (53%) of our respondents considered themselves to be owner of residual tissue. In other research, only 10%[31] or 23%[5] of patients stated that they retained ownership over tissue removed at surgery. Our respondents did not interpret 'ownership' legally; they thought that they had the right to be informed about research findings and incidental findings. Both aspects are problematic, the latter can even be considered a threat to genomic research[34] and guidelines should be formulated.[35–38]

'Commercial' research was rejected by most respondents, which differs from results by others.[22,29] Most respondents considered 'commercial research' as the opposite of 'research' from which the society as a whole benefits. This may indicate that the importance of some types of commercial research for the advancement of the medical sciences need to be communicated to patients more clearly.

Our respondents wished to be informed about tissue storage and its use in research, this preference is at odds with the way the current 'opt-out' regimen in the Netherlands is put into practice. Information is available in leaflets but it is not actively offered to patients. Dutch pathologists and epidemiologists[2,3] fear that a 'one-time consent' regimen would delay or inhibit research or causes selection bias.[39] The report of the Dutch Royal Academy of Sciences[40] advised 'opt-out', largely based upon concerns that obtaining 'one-time general consent' would involve so much effort from health care workers that a substantial non-response would result, which would create a bias in the tissue collections available for research.[9,39]

Recent international publications discuss the question whether 'one-time consent'[6,7] is sufficient for research with remaining tissues or that more control should be offered (i.e. the option to give consent for specific research).[9] The advocates of 'one-time consent'[6,7] argue that 80% of patients prefer this regimen, almost all patients agree to research with tissue and that there are no significant differences between groups according to ethic background or age and educational level. Helft et al.[9] however, show that 'one-time general consent' did not provide enough control for a significant minority, especially lower educated patients, older patients and patients from non-Caucasian origin.

Obtaining fresh consent is considered to be an extraordinary measure[41] but the increasing importance[42] of residual tissue for research may make a request for consent to include the tissue in biobank research appropriate. Many respondents want to keep some measure of control over future uses of tissue but if patients know research is well regulated and to the benefit of future patients, re-consent is given. Consent from relatives in case the donor has died is considered unnecessary.

When interpreting the results of our study, its strengths and limitations should be considered. Advantages of this study include a high response rate, especially when considering that we asked fresh consent of patients who had surgery 10 years ago. The study group was relatively small and did not allow extensive subgroup analysis, although it was large enough to give an exploratory insight into the influence of patient characteristics on preference for consent regimen.

During the interviews, our respondents suggested a 'mixed model': short verbal information about storage and use in research and the option to read more in an information sheet (with the possibility to opt-out). The on-going debate between 'one-time general consent' and 'opt-out' does not appear to represent patient wishes; for them the important question is not how they can give consent but rather how they are informed. Our respondents wanted to ascertain that patients know their tissue is stored and used, this can be done in an 'opt-out' regimen, while it is not necessarily secured in a 'one-time consent' regimen. Because of the worries about commercial uses of tissue, it appears to be important to inform patients much better. The availability of tissue for research depends on trust and cooperation of patients and these can be maintained by informing patients, so that they at least know they are 'in an opt-out regimen'.

Authors contributions

E.V., M.K.S., N.K.A., .M.K. and F.E.V.L. designed the research protocol; E.V. drafted the article; all authors critically evaluated the article and approved the final version for publication.

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The Cancer Genomics Centre had no role in the development of the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication.

Conflict of interest statement

None declared.

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REFERENCES

1. Oosterhuis JW, Coebergh JW, Van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer* 2003;**3**(1):73–7.
2. van Diest PJ. No consent should be needed for using leftover body material for scientific purposes. *BMJ* 2002;**325**(7365):648–51.
3. Coebergh JW, Van Veen EB, Vandenbroucke JP, van Diest P, Oosterhuis W. One-time general consent for research on biological samples: opt out system for patients is optimal and endorsed in many countries. *BMJ* 2006;**332**(7542):665.
4. Furness P. Consent to using human tissue. *BMJ* 2003;**327**(7418):759–60.
5. Bryant RJ, Harrison RF, Start RD, et al. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *J Clin Pathol* 2008;**61**(3):322–6.
6. Wendler D. One-time general consent for research on biological samples. *BMJ* 2006;**332**(7540):544–7.
7. Pentz RD, Billot L, Wendler D. Research on stored biological samples: views of African American and White American cancer patients. *Am J Med Genet A* 2006;**140**(7):733–9.
8. Caulfield T, Upshur RE, Daar A. DNA databanks and consent: a suggested policy option involving an authorization model. *BMC Med Ethics* 2003;**4**:E1.
9. Helft PR, Champion VL, Eckles R, Johnson CS, Meslin EM. Cancer patients' attitudes toward future research uses of stored human biological materials. *J Empirical Res Human Res Ethics* 2007;**2**(3):15–22.
10. Furness PN, Nicholson ML. Obtaining explicit consent for the use of archival tissue samples: practical issues. *J Med Ethics* 2004;**30**(6):561–4.
11. Van Veen EB, Riegman PH, Dinjens WN, Lam KH, Oomen MH, Oosterhuis JW. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer* 2006;**42**(17):2914–23.
12. Arnason V. Coding and consent: moral challenges of the database project in Iceland. *Bioethics* 2004;**18**(1):27–49.
13. Tutton R, Kaye J, Hoeyer K. Governing UK Biobank: the importance of ensuring public trust. *Trends Biotechnol* 2004;**22**(6):284–5.
14. Lin Z, Altman RB, Owen AB. Confidentiality in genome research. *Science* 2008;**305**(183):441–2.
15. OECD. Draft guidelines for Human Biobanks and Genetic Research Databases; 2008.
16. Dutch Act on the Medical Treatment Contract. <http://www.dutchdpanl/documenten/en_inf_subj_Confidentiality_Medical_Data.shtml> 2008 September 25 2008.
17. Federation of Medical Scientific Societies. Code for Proper Use of Human Tissue. Code for Proper Secondary Use of Human Tissue in the Netherlands. Rotterdam: Federation of Medical Scientific Societies (FMWV); 2002.
18. Olsthoorn-Heim ETM, Gevers JKM. Genetic research with stored human tissue; a coding procedure for optimal use of information and protection of privacy (comment) [Genetisch onderzoek met opgeslagen lichaamsmateriaal: een coderingsprocedure met optimaal gebruik van informatie bij behoud van privacy (commentaar)] [in Dutch]. *Ned Tijdschr Geneesk* 2004;**148**(25):1263.
19. Schmidt MK, van Leeuwen FE, Klaren HM, Tollenaar RA, 't Veer LJ. Genetic research with stored human tissue: a coding procedure with optimal use of information and protection of privacy. *Ned Tijdschr Geneeskd* 2004;**148**(12):564–8.
20. Schmidt MK, Tollenaar RA, van Leeuwen FE, van't Veer LJ. Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. *J Clin Oncol* 2007;**25**(1):64–9.
21. Schmidt MK, Vermeulen E, Tollenaar RAEM, Veer Lv't, Leeuwen FEv. Regulatory aspects of genetic research with residual human tissue: effective and efficient data coding. Submitted for publication.
22. Jack AL, Womack C. Why surgical patients do not donate tissue for commercial research: review of records. *BMJ* 2003;**327**(7409):262.
23. Stegmayr B, Asplund K. Informed consent for genetic research on blood stored for more than a decade: a population based study. *BMJ* 2002;**325**(7365):634–5.
24. Wheeler J, Agarwal M, Sugden J, Bladon M, Quirke P. Experiences from the front line – routine consenting of surplus surgically removed tissue. Without investment by the NHS fully informed consent for all is not available. *J Clin Pathol* 2007;**60**(3):351–4.
25. Malone T, Catalano PJ, O'Dwyer PJ, Giantonio B. High rate of consent to bank biologic samples for future research: the Eastern Cooperative Oncology Group experience. *J Natl Cancer Inst* 2002;**94**(10):769–71.
26. Chen DT, Rosenstein DL, Muthappan P, et al. Research with stored biological samples: what do research participants want? *Arch Intern Med* 2005;**165**(6):652–5.
27. Hamajima N, Tajima K, Oya H, et al. Patients' views on residual blood use for research purposes. *Jpn J Cancer Res* 1998;**89**(3):341–5.
28. Hamilton S, Hepper J, Hanby A, Hewison J. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics* 2007;**33**(4):229–33.
29. Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Genetic research and donation of tissue samples to biobanks. What do potential sample donors in the Swedish general public think? *Eur J Public Health* 2005.
30. McQuillan GM, Pan Q, Porter KS. Consent for genetic research in a general population: an update on the National Health and Nutrition Examination Survey experience. *Genet Med* 2006;**8**(6):354–60.
31. Start RD, Brown W, Bryant RJ, et al. Ownership and uses of human tissue: does the Nuffield bioethics report accord with opinion of surgical inpatients? *BMJ* 1996;**313**(7069):1366–8.

32. Medical Research Council. *Public perceptions of the collection of human biological samples*. Medical Research Council; 2000.
33. Hock YL, Balachandar C, Dicken S, Bayley C, Ramaiah S. Patients' perspective of pathology specimens. A prospective study. *J Clin Pathol* 2005;**58**(8):891–3.
34. Kohane IS, Masys DR, Altman RB. The incidentalome. A threat to genomic medicine. *JAMA* 2006;**296**(2):212–5.
35. Wolf SM, Paradise J, Caga-anan C. The law of incidental findings in human subjects research: establishing researchers' duties. *J Law Med Ethics* 2008;**36**(2):361–83, 214.
36. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med Ethics* 2008;**36**(2):219–48, 211.
37. Lawrenz F, Sobotka S. Empirical analysis of current approaches to incidental findings. *J Law Med Ethics* 2008;**36**(2):249–55, 211.
38. Van Ness B. Genomic research and incidental findings. *J Law Med Ethics* 2008;**36**(2):292–7, 212.
39. Junghans C, Feder G, Hemingway H, Timmis A, Jones M. Recruiting patients to medical research: double blind randomised trial of "opt-in" versus "opt-out" strategies. *BMJ* 2005;**331**(7522):940–4.
40. Royal Dutch Academy of Sciences. *Foresight committee on multifactorial diseases in the genomics age*. *Multifactorial diseases in the genomics age*. Amsterdam: Koninklijke Nederlandse Akademie van Wetenschappen; 2006.
41. Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J* 2007;**30**(2):373–82.
42. Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *New Engl J Med* 2008;**22**:22.