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Designing a DCE to outlay patients' and the publics' preferences for genetic screening in the treatment of depression

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Health Economics Papers
2007:1

UNIVERSITY OF SOUTHERN DENMARK

Content

Foreword

The present working paper deals with the method of stated preferences, one among several used to measure benefits of health care interventions.
In her paper Louise Herbild uses discrete choice experiments (DCE) which specifically allows an assessment of those factors explaining and affecting choices. The method is applied to genetic screening in the treatment of depression.
In the institutes research programme, the methods of stated preferences, and particular the DCE, is one of the focus areas.

The paper has been presented and discussed at the NHESG (Nordic health Economists' Study Group) meeting in Copenhagen, August 16th–17th 2006, and at the Economic Evaluation in Genetic Testing's workshop in Oxford, UK, November 23rd–24th 2006.

The paper has been completed while Louise Herbild was researcher at DSI Danish Institute for Health Services Research.

Terkel Christiansen

1. Introduction

1.1. Background

Pharmaceutical treatment of depression is characterized by problems of adverse side-effects and non-response. Polymorphisms in the genes for the cytochrome P450 enzyme system (CYP450) in the liver have been known since the late seventies (1), and as this enzyme system plays a key role in the elimination of the lipophilic antidepressants, it might improve treatment response if a pharmacogenetic treatment strategy with a genetic test for relevant polymorphisms were introduced.

Screening for polymorphisms in the genes for the CYP2D6 enzyme (debrisoquine hydroxylase), which is part of the cytochrome P450 system, has the potential to improve pharmaceutical treatment for those depressive patients who have significant changes in the genes for this enzyme. These patients either have an increased risk of suffering from adverse side-effects, due to a decreased ability to metabolize pharmaceuticals, or they have an increased risk of not getting an effect of their treatment, due to increased metabolism. Treatment could be improved by adjusting dosage according to patients' genotype.

The focus of this paper is on elicitation of preferences for the introduction of a genetic test for polymorphisms in the CYP2D6 gene, and more specifically the use of focus group interviews to inform the design of discrete choice experiments (DCE) that can help explain those elements affecting choices in a treatment situation.

1.2. Discrete Choice Experiments (DCE)

Discrete choice experiments (DCE) belong to the branch of stated preference methods, from which values of goods that cannot be purchased in regular markets can be obtained. Stated preference techniques rely on respondents' stated willingness-to-pay (contingent valuation) or choices in a *hypothetical market situation* (DCE) (2). Because of the hypothetical nature of the choices, it is crucial that the scenario outlining the market situation, which the respondents are asked to hypothesize, describes exactly what the respondents are to value, and that the respondents assume that it describes exactly what we want them to value, as this is the foundation of the resultant WTP value derived (3).

When conducted properly DCE's allow assessments of which incremental changes in attributes that are significantly relevant for users – in other words, which value components that can explain and affect choices.
Building on the set of coefficients estimated for the model parameters, a compensation variation measure that conforms with demand theory can be derived using the formula representing the marginal rate of substitution between monetary (the marginal utility of income) and non-monetary attributes coefficients (relevant elements of the treatment of depression).

In a DCE respondents are asked to state their preferred choices between two (or more) scenarios by comparing several attributes (4).

It is assumed that the value of any good can be broken down and explained by its different parts or attributes (as it is called in DCE's). An example of a choice-set with four attributes is shown in example 1.

Example 1: Choice-set from a discrete choice questionnaire on preferences for genetic testing.

In case you needed pharmaceutical treatment for a severe depression, and you were told that you only had 1/6 chance of getting improved treatment response with a genetic test (as illustrated in the column below on the right), which one of the two scenarios would you choose?

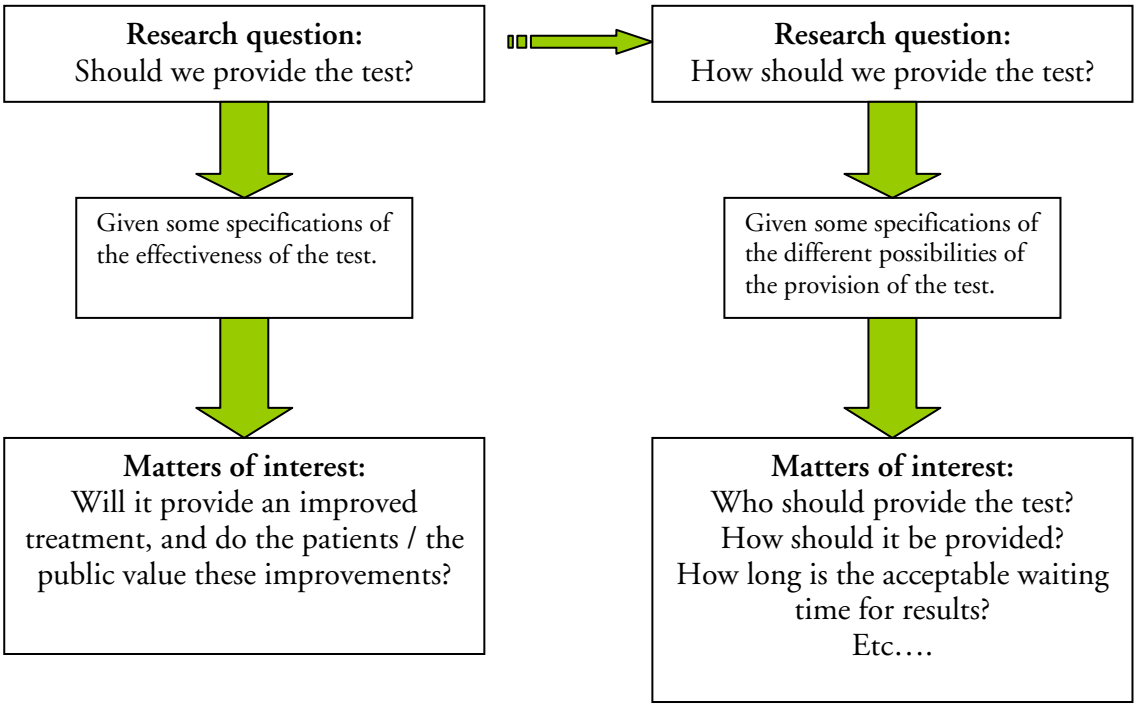
	Treatment without test	**Treatment with the test**
Number of shifts of pharmaceutical agent:	3	2
Time with symptoms before the medicine works:	3 months	2 months
Time with dosage adjustments, free of symptoms but with adverse side-effetcs	3 months	1 month
You have to pay: (expenses for medicine remains the same)	0 d.kr.	4000 d.kr.

I would chose: Treatment without the test_____. Treatment with the test____.

1.3. Preferences in DCE

A genetic test for CYP2D6 polymorphisms has been introduced in one Danish county and is currently considered implemented in others (5-9). Preferences for *the introduction* of test have therefore been emphasized as opposed to *the delivery* of the test. The latter would have been likely to include attributes on waiting times for test results, level of information, whether a nurse, GP or specialist should do the test, a price, etc. Eliciting willingness to pay (WTP) for pharmacogenetic tests' (PGx), introduction and delivery are sometimes used interchangeably or mixed with an opt-out possibility (in case the scenarios describing possibilities for delivery does not match the preferences of the respondents). The opt-out possibility causes analytical problems as well as problems of interpretation. In this project it has been found that the distinction between preferences for introduction of the test and preferences for delivery of it might not be trivial. Each depends on different questions of interest, but as should become obvious in the cause of this paper, the distinction does also cause problems related to the design of the DCE. Figure 1 below illustrates two cases.

Figure 1: Two ways of using DCE's for PGx's.



In the first case (on the question of offering the test) the way of delivery is fixed, whereas in the scenario on the question of delivery, effectiveness of the test is fixed. As mentioned, effectiveness of the test is also sometimes included in the scenario on delivery but then with an opt-out option. In both cases an explanation of the context in which choices should be made as well as an explanation of included attributes is required.

1.3.1. Construction and specification of the scenarios

"The central problem in a [stated preference] study is to make the scenario sufficiently understandable, plausible and meaningful to respondents" (10)(p. 73).

The construction and specification of the scenarios is important in order to avoid two important biases, which might occur as a result of specification choices. These include hypothetical bias and strategic bias. The first occurs when responses of the study do not represent actual valuations and the second when there are elements which encourage 'gaming' of the exercise.

Smith et al. (10) outlines two primary goals for specification of the scenario in a stated preference survey:

One has to ensure that the respondents clearly understand the characteristics of the commodity being valued and the context in which it is offered, and;

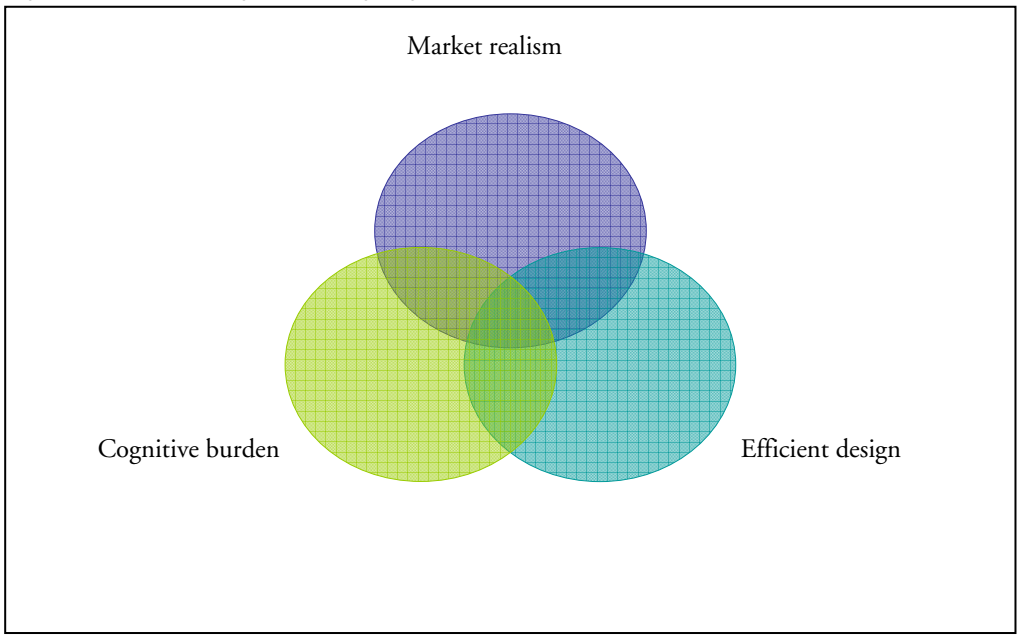
One has to ensure that the respondents find the market situation plausible.

The commodity or service in question therefore has to be described and all relevant attributes need to be specified, such that information gaps will not be filled in with guesses by the respondents. Guesses or assumptions are likely to differ across individuals, and the obtained WTP estimates will be biased.

If respondents are valuing some else, than what is intended due to insufficient specification of the scenario, this is called scenario misspecification. Three issues are important with respect to this.
Theoretical misspecification refers to a situation in which the scenario as specified by the researchers is incorrect either in terms of economic theory or in terms of policy relevance.
Amenity misspecification is where the commodity, as perceived by the respondents, is in fact different from that intended.
Third the perceived *context* may differ from that intended.

In terms of designing a DCE, the issue of specifying the hypothetical market situation as thoroughly as possible has to be weighted against problems of the cognitive demands, this poses on the respondents. At the same time efficiency of the design has to be taken into consideration (11;12). This balancing act can be illustrated as in figure 2 below.

Figure 2: The balancing act in designing a DCE.



Designing a DCE to elicit patients and publics' preferences for introduction of a genetic test screening for polymorphisms in the gene for the CYP2D6 enzyme, this has been a major challenge, and it is discussed in further details in chapter 5.

1.3.2. CYP2D6 genotypes

In order to specify the scenarios as optimal as possible and obtain valid and unbiased estimates of the WTP value from respondents, it is recommended to use pilot studies and focus group sessions to consider different views from experts, users and the general population. These interviews have been guided by available literature on the influence of the relevant genetic polymorphisms. This evidence is described below, while the focus group interviews are explained in chapter 3 and 4.

Papers on the gene for the CYP2D6 enzyme showed that a number of polymorphisms have been found, making up four different genotypes characterized by either increased metabolism of pharmaceuticals

(ultra-rapid metabolisers (UM)), slightly reduced (intermediate metabolisers (IM)) or complete inability to metabolize (poor metabolisers(PM)) and then a group of "normal" metabolisers (efficient metabolisers (EM)) (1;13-15).

There is a wide population-dependent variety on the prevalence of the different genotypes. This is shown in the table below, where the frequency of people with increased metabolic capacity (UM) is shown for different European countries (13). In general there is a tendency that the frequency of these ultra-rapid metabolisers increases as one moves south, with a maximum registered frequency of 30 % in Ethiopians. The genotype is essentially absent in Asians (13).

Table 1: Frequency of ultra-rapid metabolisers (UM) in different European countries.

Country	Frequency UM	Country	Frequency UM
Austria	4 %	**Greece**	10 %
Belgium	3 %	**Holland**	3 %
Denmark	1 %	**Italy**	10 %
England	3 %	**Norway**	1 %
France	4 %	**Portugal**	10 %
Finland	1 %	**Spain**	10 %
Germany	4 %	**Sweden**	1 %

Ref: Ingelman-Sundberg, 2005 (13).

Different studies do however report different estimates in Caucasians, and there does not seem to be any consensus regarding which are the correct ones. Table 2 below shows which frequencies are reported in different studies. This list is not exhaustive.

Table 2: Frequencies of genotypes among Caucasians reported in different studies.

Study	UM	EM	IM	PM	All
Rasmussen et al. (2006)(16)	3,1 %	80,1 %	8,4 %	8,4 %	.
De Leon et al. (2006)(17)	.	.	.	7 %	.
Heller et al. (2006)(18)	2-10 %	.	.	5-8 %	.
Ingelman-Sundberg (2005)(13;14)	5,5 %*	.	.	7 %*	25-30%*
Ingelman-sundberg (2005)(13)	1-2 %***	.	.	.	.
Kawanishi et al. (2004)(19)	0,8-1 %	.	.	6-10 %	.
Zackrisson et al. (2004)(20)	1-7 %	.	.	8,5 %**	.
Kirchheiner et al. (2001)(1)	.	50 %	40 %	10 %	.
Raimundo et al. (2000)(21)	.	.	10-15 %	.	.
Bathum et al. (1998)(22)	0,8 %	.	.	.	.

* Europeans. ** Observed among a control population of Swedish blood-donors. *** Reported for Northern Europeans.

The indecisiveness with regards to the "correct" distributions of the different genotypes causes problems with regards to the design of the DCE's for this project. In order to maximise theoretical validity as well as avoid amenity misspecification, it is important that the scenarios facing the respondents are correct in terms of the probabilities of belonging to one of the deviant genotypes (e.g. PM, IM or UM) and hence getting an effect from a genetic test. It is not unlikely that depressive patients have another distribution than the general population, and the theoretical correct estimate for the genotype frequencies would hence be obtained from a study amongst the target patient group for this study, e.g. Danish patients with a moderate to severe depression.

Estimates on a defined population of moderate to severely depressed patients are not available[1], but close substitutes, from the county in which genetic screening for CYP2D6 polymorphisms has been implemented in routine clinical practice at the hospitals, have been published (16). Within a group of psychiatric patients treated in Vestsjællands County (n=225) as well as a group of healthy volunteers (n=122), differences in the frequencies of the different genotypes could not be established. The ultra-rapid metabolisers (UM) with increased ability to metabolize constituted 3,1 % of the study population. The poor metabolisers (PM) with no ability to metabolize pharmaceuticals was found with a prevalence of 8,4 % among patients from Vestsjællands County and the prevalence of those with decreased ability (intermediate metabolisers (IM)) was 8,4 % (1). These estimates are based on a relatively small population (n=347), but are considered to be the best estimates available and was chosen for the DCE.

Table 3: Genotype frequency in a population and expected treatment response without genetic screening.

	Prevalence in a Danish population	If treated with ordinary dosages*
Poor metabolizers (PM)	8,4 %	High risk of toxicity
Intermediate metabolizers (IM)	8,4 %	Increased risk of toxicity
Efficient (normal) metabolizers (EM)	80,1 %	Response as expected
Ultra-rapid metabolizers (UM)	3,1 %	Decreased chance of effect

* Treatment response if treated with substrates that are primarily metabolised by CYP2D6.
Ref.: (16).

1.3.3. CYP2D6 genotypic treatment response

From practitioners within psychiatry it was told that therapeutic drug monitoring (TDM) is used in some settings to control plasma-concentration levels for psychiatric patients, basically making a genetic test superfluous. In spite of this the Danish county (Vestsjællands Amt) has introduced routine screening for all psychiatric inpatients using the genetic test (23) and recommendations have been made that other counties should do the same (5;6;8;9). The reason for this seems to be that TDM both requires repeated blood-samples and is not used systematically but rather in few difficult cases[2]. Further arguments pro TDM and against the genetic test are, that benefits of screening for CYP2D6 polymorphisms are complicated by the fact that it isn't all anti-depressants that are primarily metabolized by the gene (1;1;24). Due to the partly unknown and complex nature of psychiatric diseases, response to pharmaceuticals is also affected by individual differences in pathways, receptors and disease pathology (1;25-28). Hence in spite of relatively high prevalence of diverging genotypes, it is estimated that only 2-5 % of all patients will get an improved effect if genotyped. This estimate is not based on explicit studies or trials, but is a qualified guess by Magnus Ingelman-Sundberg from the Division of Molecular Toxicology at the Karolinska Institute in Stockholm, who has conducted a wide range of research on the topic (13;13;14;29;30).

Retrieved papers confirmed that medicated patients with a decreased ability to metabolize their medication (poor metabolisers (PM)) will be likely to suffer from heavy side-effects, if dosage adjustment does not take their metabolizing capacity into account. Even though therapeutic drug

[1] A HTA are currently commenced at Bispebjerg hospital in Copenhagen which is expected to provide similar estimates for a population of Danish schizophrenic patients. For further detail contact the author.
[2] One other Danish County (Aarhus) has implemented TDM in routine clinical practice on an experimental basis.

monitoring (TDM) could potentially capture these patients, one study showed that this was far from the case always (31). PM's and IM's get toxic levels of their pharmaceutical agents, if they are treated with pharmaceuticals that are metabolized by the CYP2D6 at standard dosages (1). This will be most pronounced for PM patients, and toxicity results in problems of adverse side-effects of which some can be lethal (20;32;33).

A German study by Rau et al. (34) found that in a subpopulation of psychiatric patients reporting adverse effects, the proportion of PM's was 4-fold higher than in the general population, suggesting that these genotypic specific patients' risk of suffering from adverse side-effects is increased. Adverse effects were marked enough to lead to a termination of treatment in nearly 80 % of patients (34).
Another Dutch study found that the risk of a plasma concentration above the therapeutic range was increased for PM's (OR 33.1) and IM's (OR 8.2) relative to patients with a normal metabolizing capacity (extensive metabolisers (EM)) using antidepressants (31). This was the case in spite of the fact that one of the inclusion criteria's for participating in this study was that patients had had TDM. Although the genetic test could be claimed redundant, as TDM is in theory capable of giving similar results, this evidence supports the clinical relevance of conducting a genetic test anyway.

In the German study by Rau et al. (34) non-responders were also identified, and within this subpopulation of patients there was an 5-fold increase in the proportion of ultra-rapid metabolisers (UM), compared to what would have been expected if the effect of multiple alleles did not affect clinical outcome (34).

In spite of massive evidence of the effects of polymorphisms in the CYP2D6-gene, and a relatively inexpensive way to test these, the effects of the test have not been tested in larger prospective trials, and only one study has looked at cost-implications of using the test and been able to show a trend towards cost-savings (35).
Evidence suggests that those areas of antidepressant treatment, the genetic test would be likely to impact, would be on time passed before an adequate pharmaceutical treatment and an appropriate dosage for this is found and an acceptable effect obtained. These therefore constituted candidate-attributes to be included in the discrete choice experiments (DCE) and were to be further discussed in the focus group sessions.

As described earlier, it has been recommended and is still discussed politically whether it would be relevant to offer all psychiatric patients a genetic test for CYP2D6 polymorphisms, before initiating pharmaceutical treatment. If this is decided the next relevant question would be to ask the question of how the test should be offered – e.g. the distinction between the two research questions raised in figure 1. Since it has not been decided to implement the test nationwide yet, the most relevant question would still be, whether patients would want the test, or if they'd prefer current practice. The difference in terms of all relevant *outcomes* of the test as compared to current practice should therefore be specified in the choice-sets, if they are important to the patients.

One of the challenges in this project is that evidence on the effectiveness of the test has not yet been established. This was one the reasons why a DCE framework was chosen, as it allows investigation of

preferences for incremental changes in included attributes. Hence in spite of lack of sound evidence, the DCE will shed light on how much changes in the chosen attributes are valued. Essentially this does require that the used estimates for the DCE are within a realistic range of the true estimates. Until these are available, the best way to specify the scenarios therefore seems to be to use those estimates that are available, as well as experts' opinion on the matter.

2. Methods

2.1. Literature search

Literature and expert opinions were used to inform the development of the first interview guide as well as give an impression of potential benefits of the genetic test.

A preliminary literature search was conducted in March 2005 in the database TDNet, searching for titles which contained the words *pharmacogenetic, depression*, *depressive*, *antidepressant*, *CYP2D6*, *Cytochrome P450* or *CYP450.* At the same time a regularly weekly search were set up, searching for new titles containing the same words. It was assumed that papers referring to studies investigating specific drugs and their treatment consequences given a specific genotype would be captured, using these search terms, and searches was therefore not conducted using specific names or substances of relevant drugs[3].

Papers referring to studies on effects of the genetic test and implications of having a certain genotype as well as costs or savings of introducing the test were retrieved. Papers referring to problems of adverse side-effects of antidepressants' as well as other papers on the treatment of depression were reviewed as well. References in these papers on other relevant studies or articles were used to find additional papers.

2.2. The focus group interviews

Three focus group interviews with current and former patients were conducted in order to ensure that the attributes in the DCE are those who are relevant, and that all information on relevant aspects of these attributes will be included in the questionnaire in order to avoid misspecification and hypothetical biases. The basis for the interviews was information obtained from the literature search as well as opinions from experts on expected benefits of a test. This was in order to avoid theoretical misspecification of the scenarios, and the purpose of the focus group interviews were then to avoid amenity and context misspecification. The process is illustrated in figure 3 below.

Figure 3: The process used to design the DCE questionnaire.

[3] Drugs primarily metabolized by the CYP2D6 enzyme include: Amitriptylin, Chlorpromazin, Citalopram, Clomipramin, Doxepin, Fluoxetin, Fluvoxamin, Haloperidol, Imipramin, Maprotilin, Mianserin, Nortriptylin, Paroxetin, Perphenazin, Risperidon, Sertindol, Trimipramin, Venlafaxin, Zuclopenthixol.

The interview guide was designed such that problems of the pharmaceutical treatment of depression could be discussed, moving from more general questions to more specific ones, as recommended in the theoretical literature on qualitative research interviews (36). This would then also include issues of lack of effects and problems of adverse side-effects if they were of importance. The interview guide used for the first interview is translated and shown in appendix.

The focus group interviews were conducted in an iterative manner such that topics arising from the first interview constituted the bases for the next one and so forth. It was initially decided that additional focus group interviews would be held as long as further substantial information could be expected by conducting additional ones (36). This expected marginal information gain was traded against disadvantages of asking additional respondents among the limited number who agreed to participate in the overall study, which also encompasses the discrete choice experiments.
Three interviews were conducted. They were all recorded and replayed subsequently by both the author and an assistant (sociologist) in order to withdraw essential parts of the interviews. None of the respondents participated more than once.

2.2.1. Recruitment of participants

Participants for focus group interviews and discrete choice experiments were recruited using several sources. An add was put in the electronic newsletter published from the pharmaceutical company of Lundbeck, who produces antidepressant medicines. Another add was put on Lundbeck's website for depressed people called DepNet, and finally members from the patient association for depressive people in Denmark (Depressionsforeningen) was emailed, if they had agreed to participate in research activity when joining the patient association. Respondents were invited to participate in both an individual interview and a focus group interview, but some requested only to participate in the individual interview. A total of 88 persons responded, of which all wanted and were eligible to participate in the study.
Respondents were included in the study if they were between the ages of 18 and 65, and if they had once in their life time been diagnosed with a depression of any kind and had had antidepressant pharmacotherapy. No emphasis was put on the number of times they'd had a depression, number of pharmaceuticals given or specific sort of diagnosis.

Participants were briefly informed of the overall goals of the project in the adds and the inclusion criteria as well as what would be expected of them if they decided to participate. If they applied to be included in the study they were send a standard letter with further information about the study and its context. No rewards or compensation for time spend on the focus group interviews were offered, but they were told that sandwiches and beverages would be served at the meetings.

Participants were divided into geographical areas consisting of the eastern part of Denmark (Sjælland), the central part (Fyn) or the western part (Jylland). For the first focus group interview all listed participants from the capital in the eastern part of the country were invited. For the next all respondents

from the near Århus area were invited and for the last interview respondents from almost all over Jutland were invited.

2.2.2. Conducting focus group interviews

Focus group interviews have been defined as *"carefully planned discussions designed to obtain perceptions in a defined area of interest in a permissive, non-threatening environment"* (36) (p. 5). By *carefully planned* some refers to the considerable research on the topic of interest that ought to be conducted before interviews are carried out (37). This does however depend on the purpose of the interviews and the research questions asked, as focus group interviews today are used for a number of different purposes.
Focus group interviews can be beneficial at practically any point in a research project. It can be used to:
obtain general background information about the topic of interest,
generate research hypotheses that could be the object for more quantitative testing later on,
stimulate new ideas and concepts,
diagnose potential areas with problems in new services, programmes or products or just giving impressions of these,
discuss results obtained at earlier stages in a research project and the interpretation of these.
The first four of these can be seen as the purpose for using focus group interviews in this project.

The principles of focus groups interviews has been outlined as follows: 1) the group is an assembly of target respondents whose points of view are requested to address a single topic; 2) the group is small, 6-12 participants, and it is relatively homogeneous; 3) a trained moderator with prepared questions and probes sets the stage and induces participants' responses; 4) the goal is to elicit the perceptions, feelings, attitudes and ideas of participants about a selected topic; and 5) focus groups do not generate quantitative information that can be projected to a larger population (38).

The origin of focus group interviews is somewhat unclear. It has been suggested that focus group interviews were first used in the late 1930'ies by social scientists (36). Some claims it had its first breakthrough in 1941 when it was used to explain uptake on different radio programs (39) and yet others believe that it has its origin in marketing research and not the social sciences (40). A recent publication seems to point at Merton and Kendall's first publication on the methodology of focus group interviews (1946) and a following publication on the technique (Merton, Fiske and Kendall 1956) as well as market research pioneer Alfred Goldmans paper "The [focused] Group Depth Interview (1962) as the foundations for what has become a widely used technique within qualitative research (39).

Focus group interviews belong to an era of qualitative research from which other kinds of group interviews as well as individual interviews also come. What distinguishes focus group from an individual interview is the presence of group interaction in response to the researcher's questions. This has been postulated to enable the researchers to gather data which could not have been obtained in other ways (41), although there does not seem to be any support for this postulate (39).
Compared to other kinds of group interviews, for example Delphi panels which seeks consensus on the topic in question, focus group interviews are concerned with diversity in opinions and perceptions on the topic. The discussion within the group is supposed to act as an inspiration for participants making them aware of things that they had not thought about previously.

"At the beginning of a focus group, […] participants will not be immediately able to express all their feelings or motivations on a topic. As they hear others talk, however, they can easily identify the degree to which, what they are hearing, fits their situation. By comparing and contrasting, they can become more explicit about their own views" (40)(p. 17).
As such, the focus group interview is beneficial as the exchange of opinions between participants help them to clarify just what their attitudes towards the topic are.

In contrast to quantitative research, qualitative research and focus group interviews are not meant to search for "the truth" of a particular situation or event, they are rather aimed at shedding light on and bringing meaning to things. The method and modes of analysis imply a certain extent of subjectivity, which could be argued exists' just as much in the design-stage of any sort of quantitative research (42). The analysis of data obtained from focus group interviews, consisting of both recordings and notes about attitudes and non-verbal communication, is therefore recommended to be systematic, sequential, verifiable and continuous, in order to reduce potentials of biases in the interpretation process (36).

Focus group interviews are based on what is sometimes called "the funnel approach", where questions raised for discussion in the group moves from more general to more specific ones. In this way participants are guided to think about the object for the interview and through discussion and more specific questions, the topic is narrowed down (36).
The usefulness and validity of focus group data are however affected by the extent to which participants feel comfortable about openly expressing their ideas, opinions and views on the topic of interest (39). There exists a wealth of literature concerning group dynamics and all things that are likely to affect this and the results of a focus group interview. These include socio-economic characteristics such as gender, ethnicity, age, income and education, but also issues about clothing, weight and personality characteristics such as temper and social skills. This is not an exhaustive list and interested readers are referred to Stewart (2007) for further information (39).
The essential thing is to chose participants that are homogeneous with respect to some characteristics (those that will enable group discussion and dynamics) but still not too homogenous, as it will hinder discussion if all participants agree with each other and have congruent opinions on the topic of interest. There has been some discussion with regards to whether one should try and avoid having people, who know each other, in the group or whether this could actually be beneficial. It seems to depend on the research question and the cultural setting for the interviews, and again the essential thing seems to be that participants feel comfortable (39). In situations where it will not possible to exercise influence on the composition of the group, it will instead be the responsibility of the moderator to ensure that the group members feel comfortable and are willing to express themselves (39).
Some researchers have also been investigating the influence of the physical environment for focus group interviews and the timing of these with regards to group dynamics and results. The results from these studies seems to indicate that one should be aware of the potential influences of these things and avoid relying on any sort of recommendations with regards to location and timing (39). Hence the essential issues regarding set up and conduction of focus group interviews seem to be that the moderator is aware of potential threats that might compromise the comfort of the participants and willingness to speak in the group.

The results from the three focus group interviews are presented below.

3. Results from the focus group interviews

In the first interview, 18 respondents from the main capital area were invited to participate. 11 accepted the invitation. Non-responders were sent an additional invitation, and a couple of days before the interview took place, reminders were sent to those, who had already agreed to participate. 9 actually showed up for the interview. This practice was used for the other focus group interviews as well.

3.1.1. First impression of the pharmaceutical treatment

In the first interview respondents were asked a series of open semi-structured questions. After a few opening questions, in order to ensure that everybody felt comfortable about speaking in front of the others (36), the group was asked to comment on their first impression of medical treatment. What worked well and what didn't. It became obvious that it was quite difficult to separate the medical treatment from the rest of the treatment (e.g. cognitive therapy) and the question divided the group in two subgroups; one, in which the impression was rather positive, and one in which it was negative.
In the positive group the predominant impression was that respondents had confidence in their prescribing physician (whether it was their own GP or a specialist in psychiatry). Honesty and self-awareness of inadequacy of the doctor seemed to be an important aspect with regards to this, and one of the respondents described how his GP had admitted that he had no knowledge of which antidepressant to chose and instead referred the patient to a specialist. This had made him gain confidence in the GP.
In this group most respondents had also been referred and seen by a specialist within what was considered to be a reasonable amount of time.

In the other group, respondents did not have any confidence in their prescribing physician. They felt that they hadn't been given any information about possible side-effects, what effects to expect or even for how long they should wait for an effect. One of the respondents described it this way:
"I sometimes get the feeling that the doctors are choosing pharmaceuticals on the same bases as if I was a child in a candy-store and he had to choose between yellow and blue candy-drops for me" (Translated ed.).

It was also stated that as a patient you feel like you're basically participating in a lottery in which you might be given a skilled and qualified treatment or a random and uncoordinated treatment.
Another said:
"In the beginning I got the impression with this doctor that he was just testing one drug after another on me, increasing the dosage, changing again and so forth without any kind of information and seemingly also without structure" (Translated ed.).

A couple of the other respondents added to this that they'd had to look for information themselves and that it shouldn't be like that because the disease in essence usually prevents you from doing anything like this.

3.1.2. Effects and side-effects of the pharmaceutical treatment

Across the two groups the majority of respondents had had several shifts in medication before they experienced either an effect or an acceptable level of side-effects. They explained how frustrating it was to have to give up on a drug and start all over with a new one, both because of new side-effects and

because of anxiety of whether the new drug would work. One of the respondents did however point out that she had learned to think of the negative side-effects as a sign of effectiveness of her drug:
"[…] at least I can be sure it is actually working, doing something inside my body" (Translated ed.).

Another of the respondents added that she would chose the medication and side-effects at any time rather than have to suffer from depression again. This made most respondents nod in recognition.
Also the majority of respondents agreed that it was hard to know what they could actually expect from their medical treatment. One respondent said:
"I don't really know whether I dare change from the product (pharmaceutical) I'm taking now in order to hope for less side-effects,[…] could be that I'll get even worse or return to my depressive state - and that thought is unbearable" (Translated ed.).

Another respondent then suddenly said, that now the others had been talking about all of their side-effects, she had realized that she was suffering from quite a few of them. She'd just thought that it was related to stress and the disease itself, she'd never been told anything about possible side-effects or asked about them.

One of the other respondents explained, how her physician had put her on two different drugs at the same time, which she was later told actually eliminated the effect of each other. This was however not discovered until she had gotten really sick and was admitted to a psychiatric hospital, where they had greater expertise about the different antidepressants and put her on another new drug.

Most respondents also nodded in recognition when one of the respondents said that in general it seemed that every doctor had his or hers own personal favorite antidepressant drug, and if they got to se a new doctor they were likely to be put on a different antidepressant unless they'd studied and found out themselves what they thought might work best for them.

In general there seemed to be quite an issue of lack of information and wish for a higher level of expertise and specialization. Most patients didn't know whether they were given a good or bad treatment or what they should expect.

3.1.3. Confidence in prescribing physician

The next focus group interview was held in Århus in Jutland. 12 respondents had been invited and 6 participated. Two respondents who had agreed to participate were unable to attend because of a bus-strike in the Århus area.

The objective of this second interview was to explore in more detail, issues brought up in the first interview. Essentially this was the issue of legitimacy of drug choice and confidence between patient and prescribing physician, as well as problems related to shifts in medication. Respondents was also introduced to the genetic test and asked about their attitudes towards genetic screening in general as well as how they would feel about having a genetic test.

On the question of importance of confidence in the prescribing physician it turned out that there seemed to be some difference in access to specialist consultancy in this part of country, something that didn't seem to be such an issue in the Copenhagen area.
The respondents all stated that trust was an important aspect of treatment, but some of them had had to wait more than 10 months after referral to see a psychiatrist for the first time, and then none of them had the strengths to ask for another if the relationship with this psychiatrist didn't work out. One of them explained the difficulties of getting help like this:
"The best way to get good and perceived qualified treatment is to get really sick and be admitted to a psychiatric ward" (Translated ed.).

Another respondent said that she was quite sure she would have done much better, if she'd had help sooner and wouldn't have had to wait so long to se a psychiatrist that would initiate pharmaceutical treatment. She expressed that her chances of returning to a normal life and getting back to work would have been much better with more intensive help from the beginning.
This problem of access also meant that most respondents hadn't experienced the same shifts in medication as a result of shifts in prescribing psychiatrist. Also the respondents expressed they felt they didn't have the privilege of being dissatisfied if the interpersonal relationship with their psychiatrist wasn't working.
One respondent explained how he felt he'd been his own doctor with regards to the choice of medication, regulation of dosage etc.
"[I would have liked to get] some rigid and crude knowledge of what to expect from the medication".
Instead he'd had to look everything up himself on the internet in order to suggest for his GP which pharmaceutical he would like to try next.
"This situation might work for other patient groups, but when you are depressed it is exactly these kinds of things you usually just can't manage" (Translated ed.).

In the group of respondents from Århus the question of confidence was much more related to the level of information about medication than in the group from Copenhagen which also stressed that interpersonal relationship and "chemistry" between patient and doctor mattered. Respondents in Århus expressed a wish for a higher degree of specialization, such that some psychiatrist' were specialists on depression and pharmaceutical treatment for this and didn't also work within other psychiatric diseases.
"In the beginning you are very orthodox, believe in everything the doctor says and trusts him or her, but eventually you find out that in fact most of them does not know much and you have to act as your own specialist" (Translated ed.).
Another respondent agreed with this and said:
"They actually ought to offer you an education in how to be demanding within the psychiatric system when you get a diagnose of depression for the first time" (Translated ed.).

3.1.4. Waiting for test results

The genetic test was explained to respondents, and they were asked how much waiting time they'd considered as acceptable, before the results of the test were ready, and pharmaceutical treatment could be initiated.

Most respondents agreed it wouldn't matter if they had to wait for the results of a genetic test as long as they would be informed about what they were waiting for. As one of the respondents puts it:
"There is so much waiting time involved in the treatment and recovery from depression, if I would have had to wait another month in the beginning but then could have settled with just trying two different drugs instead of 6, that would seem ideal to me" (Translated ed.).

The maximum amount of acceptable waiting time did however seem to be around one month. Also respondents seemed to think that it would be natural to start with some first-choice initial drug when waiting for test results, just as would have been standard practice without the genetic test.

3.1.5. Who should do the test

Respondents were also asked who they'd prefer did the test, i.e. whether it should be their own GP or a psychiatrist, and if it would matter where it was done.
They all agreed that specific location didn't matter, what mattered was the interpretation of results:
"Results like this are not easy to explain, like if you have a broken arm, that could be explained to you by anybody, with something like this you don't have a chance in a million to know whether you've been given sufficient information or not" (Translated ed.).
This conforms very well with the statements in the first interview, about insecurity of what to expect and whether you're receiving a good treatment or not.

One of the respondents suggested that the GP could take the blood sample and send it to a highly specialized laboratory and this laboratory could then contact and explain results to either just the GP or the patient as well. Another respondent added that it could also be that you were just send a paper explaining the results and that the GP then received the same paper such that any ambiguity and questions could be dealt with.

There didn't seem to be any concern in the group with regards to the necessity of a blood sample for the test, and only one of the respondents initially expressed concern with regards to the ethics of implementing this kind of genetic screening. After some discussion in the group this concern did however seem to vanish.
In general it seemed that all of the respondents would prefer taking lowest possible dosage of pharmaceuticals that would still be effective.

3.1.6. Expenses of treatment

The group was also asked whether it would be reasonable to ask a price for this kind of genetic test. There seemed to be a general agreement that this wouldn't be of great concern, since most of them already spend many thousands every year on pharmaceuticals and cognitive therapy with psychologist.
"You have no idea how expensive it is to be in a depression. I've heard of people who stop taking their medication because they can't afford it" (Translated ed.).
Another respondent added to this:
"Money is crucial. If you have enough money you can pay to see a psychologist once or twice a week and you have the means to try out different therapist' in order to find one that suits you. I've probably spend about 200.000 d.kr. in the last five years I've been sick, - but I'm almost over it now" (Translated ed.).

This led to a discussion of what an ideal treatment strategy would be and whether the essential thing is optimized medical treatment or cognitive therapy. Some respondents thought of medication as treatment for symptoms of depression, whereas real cure for it was therapy. All but one did however agree that medicine is a necessity in order to even benefit from therapy.
Everybody also agreed that faster treatment without waiting times to see a psychiatrist would improve treatment process considerably:
"You feel so bad in the first place that it seems almost as torture to have to wait to get qualified treatment in order to get better" (Translated ed.).

3.1.7. The organization of treatment

In the last focus group interview 14 respondents from all over the Jutland area were invited. This included the two who were prevented from participating in the second interview due to the bus-strike. 6 of these accepted the invitation, but only 5 participated.
The central issues for this third interview was, besides from general questions on experiences of medical treatment and attitudes towards genetic screening, issues of waiting times and specialization.

As in the previous interview most of these patients have had to wait for a long time before they could get an appointment with a psychiatrist, and as before these patients also stated that pharmaceutical treatment of depression only constituted a little part of treatment and couldn't be separated from psychological therapy. One respondent expressed his wonder, why psychiatrist and psychologist don't work together in joint practices such that psychiatrists' deal with pharmaceutical treatment and psychologists' with cognitive treatment.
One other participant responded to this that it was her expression that it was the case in one of the hospitals where she'd been admitted a few times, and that this had been very positive. She also told she had been given psychologist's consultations twice a week free of charge at this hospital ever since she was discharged, and that she'd been given an appointment with a psychiatrist right away after the referral. A couple of the other participants then seriously began to talk about moving to this particular city.

In this focus group it was also the general impression that GP's and psychiatrists shouldn't be substitutes for each other. The psychiatrist should be a specialist with regards to pharmaceutical treatment whereas the GP should "just" handle personal things, conversations and advice etc., if he or she was not equipped for pharmaceutical therapy. Again, there was unanimity when one of the respondents stated that she really gained respect and confidence in her private GP, when she had said to her that she didn't want to handle her pharmaceutical treatment, because she wasn't competent enough, but that she would be glad to give her therapeutic consultations or just listen. This happened after she had changed her GP because the former didn't seem to have any plan or competence with regards to her medication.
"He just gave me one new product [antidepressant] after another, every now and then trying to adjust the dosage but seemingly without any coordination or plan" (Translated ed.).
This is the exact same issue as one respondent in the first interview was talking about.

3.1.8. Beliefs about genetic screening, price and organization

When respondents were asked about their opinion with regards to genetic screening for this kind of treatment, only one was sceptical:
"It might lead to some sort of a rollercoaster effect and all of a sudden you won't be able to get yourself a life-insurance" (Translated ed.).

The group agreed that it would be optimal if it would be possible just to screen high risk individuals, but they were also able to reckon the problems of how to identify these. After some discussion they agreed that it probably had something to with ignorance and that it would be possible to persuade practically every patient as long as they were adequately informed about what kind of test it was.
Respondents were explained in more detail what the test could actually benefit with and it turned out that most participants in this group had had their plasma-concentration levels monitored regularly in the beginning of their treatment course[4]. One respondent said:
"I've been lucky because now they are giving me a drug which they actually monitor in my blood whether I'm getting the right dosage" (Translated ed.).

This again seems to indicate that patients really feel insecure about their treatment and possibly would have liked if there existed some way to measure objectively whether they were given the right treatment.

Another respondent stated that he was quite sure that if he had been given the drug, which he was taking currently, which was working really well, he wouldn't have been admitted so many times.
"[…] and we're talking heavy long admittances of 22 months and more on the secured wards, and I wouldn't just have applied for early retirement pension" (Translated ed.).

Respondents were also asked how they'd feel about having to pay for a genetic test and how much they might be willing to pay. Most of them agreed that they're already paying out-of-pocket for so many other things, that if they had to pay for something more it wouldn't matter much.
"I've spend thousands on different kinds of products that did not work well, and when my psychiatrist suggested that I'd try a new one, I would just give back whatever I had left of the old drug at the pharmacy – basically throwing away money" (Translated ed.).

Another of the respondents adds to this:
"We're not even halfway through the year and already I've spend somewhere around 14.000 d.kr. (£1200) on drugs alone, and on top of this, I have expenses on psychologist consultations and physiotherapy because I have tensions all over and headaches otherwise" (Translated ed.).

The group seemed to agree that it is unacceptable that they have to pay for therapy themselves and that it's only possible to get for free if you've had a traumatizing experience. The level of frustration due to this seemed to increase as one participant told how she'd been given up by the psychiatrists – and were told that they couldn't find any suitable drug that she could tolerate, and that she should go and get some cognitive therapy instead – although she'd have to pay for this herself.

[4] Therapeutic drug monitoring (TDM) can be seen as a substitute for the genetic test. TDM does however require that several tests are done, and though it is used somewhere within psychiatry its use is far from systematic or routine.

The last part of discussion was about who should take the blood sample for the genetic test, and who should deliver results and interpret them.
There was no doubt within the group that they wouldn't care about distance or whether it was a stranger (other than own GP or psychiatrist) who did the test and delivered the results:
"As long as is it the best, most skilled people and you know they are experts within this area - that is how I would prefer it at any time" (Translated ed.).
This conforms very well with statements from the previous interviews.

At this point it was decided not to conduct any further interviews. Partly because the information gained from the last interview didn't seem to be worth doing more, but also because it would mean that additional respondents, who should participate in further focus group interviews, could get biased, and respond differently than they would otherwise have done, when they were to participate in the discrete choice experiments.
This is of course already an issue with the 20 respondents who participated in the three interviews just described and is a weakness of the project. The problems related to recruiting participants in the first place do however not leave room for any other more optimal solution.

4. Discussion

It was initially hypothesized that it would primarily be the extent of side effects, as well as time spend before an acceptable effect of medication was obtained, that made a difference for patients treated for depression. These issues have not been found to be irrelevant, but it is also the insecurity of what to expect from treatment as well as insecurity of whether patients are receiving a qualified and competent pharmaceutical treatment, that seem to matter. Patients do feel frustrated about all the different shifts in pharmaceutical product and dosage, and this seem to worsen if the process is characterized by lack of information, coordination, and the patients are getting an impression of an incompetent doctor.
The genetic test might therefore have a value of its own irrespective of its potentials to reduce number of shifts in medication and level of side-effects, if it provides patients with an assurance that the choice of drug as well as dosage is well funded. This does however seem to depend upon the level of information given, as well as the impression of competence of the prescribing doctor, and as such it falls within a grey-area between "preferences for introduction of the test" and "preferences for delivery of the test". The scenarios might suffer from misspecification if respondents presume the test is delivered in a way that would not be concordant with reality when/if the test is introduced. On the other hand, clinical practice varies between doctors and between sectors, and it might just as well lead to misspecification biases, if a context for introduction is presented in the scenarios. This also has to be weighted against problems of cognitive overload on behalf of respondents if too much information is presented.
At present the only certain improvement in the treatment process the test can deliver, is certainty that patients will receive the best technical treatment available. How information and test results are provided and used are likely to differ just as much among patients as current practice. It has therefore

been decided to stick with a stringent design concerning only introduction of the test leaving questions of information unspecified.

Another attribute falling in between the two categories of "introduction" and "delivery" that initially was considered included, was the question of waiting time for test results. The focus group interviews did however reveal that it was not important, and it was rather the way the test could be used and interpreted that seemed to matter. But the fact that respondents, who participated in the focus groups, all have been diagnosed some while back and all have experienced subsequent changes in pharmaceutical product, might have led to some ignorance of the importance of waiting time for test results. It might not be that a "new" patient, suffering from depression for the first time will feel the same. It does however not seem possible to overcome this selection bias since it is unlikely that any newly diagnosed patient would have the strengths to participate in a study like this. Besides, the fast technical development has also already provided a large reduction in waiting times from 10-15 days in the beginning of 2005 to 7 hours to 2 days at present. This might end up making an attribute on waiting time redundant, if it gets even lower and solves the problem.

The last essential attribute is related to the wish of calculating marginal willingness to pay for changes in the different attributes' levels, and consists of a cost attribute. This should cover a range from zero and up to a level that ensures that some respondents will not want the test, i.e. above an upper level of maximum willingness to pay. As some patients stated, how they spend huge amounts every year on medicine and therapy, this might be problematic, if respondents in the patient group are unwilling to trade between price-attributes and other attributes. One respondent had spent well over d.kr. 14.000 on drugs within 6 months, and this suggests that the upper limit should probably be set above this. Pilot testing of the questionnaire will be used to secure this.

It has been considered to outline the use of therapeutic drug monitoring (TDM) as a comparator in the DCE, either as a third alternative, or just as specified in the status-quo scenario. Literature as well as current treatment practice does however seem to indicate that this would be irrelevant, as it is not used systematically and even when it is used, does not capture deviant genotypes. This idea was therefore abolished.

5. Implications for the DCE

Guided by the results from the focus group interviews, the first relevant attribute to include in the DCE questionnaire seems to be the number of different pharmaceutical products that has to be tested before an acceptable level of effects and side-effects are obtained. The general impression from the interviews was that most patients had experienced 3-4 shifts, while ¼ of patients had experienced 6-8 shifts in medication without the genetic test. With the genetic test one might hope for only 1-2 shifts but this will probably depend on clinical setting and expertise of the prescribing doctor.
No evidence is currently available (41) to guide the range of this level. Experts were consulted on the matter, but most of them did not feel comfortable about giving such estimates as the treatments differ so much. One chief-psychiatrist from a larger psychiatric hospital did however state that her impression were that most patients with a moderate to severe depression had 4-5 different types of anti-depressants before they were satisfied with results, in terms of level of adverse side-effects as well as effect. This conforms well to the impression from the patients.
It is however most likely that both the patients participating in the interviews, as well as patients at a psychiatric hospital, represent a group of patients characterized by treatment difficulties. This would then affect external validity of the study. As stated with regards to recruitment of respondents for the DCE, this is however already an issue and the results from the project are likely only to be representative of patients with moderately to severe depressions.

As an alternative to an attribute on numbers of shifts, a probability of having to test more than 3-4 different pharmaceuticals before a suitable product is found, was considered. This would however also depend on what makes most sense in a clinical perspective (i.e. it might be that the threshold should be 2-3 different pharmaceuticals). Besides, studies have shown (10) that changes in probabilities within smaller ranges can be difficult for respondents to grasp. This suggests that the former will do better, if changes are small.

Because of the problems related to lack of effect-estimates or even prevalence estimates on the number of different pharmaceuticals a depressed patients could expect, it has been decided to benefit from experiences in the patient-respondent group as well as expert opinion on the matter. These are unlikely to be representative of a general depressed patient-population, but they could be representative of a group of moderate to severely ill patients. In the DCE for the patient-group it has therefore been decided to operate with a fixed comparator, constituted by each patient's own treatment experiences. This will also exclude any doubts of whether patients will be able to refrain from their own experiences when faced with hypothetical scenarios. It will not solve the problem of non-existing effect estimates on the genetic test, but with conservative reductions in attributes it would still be a clinically and politically relevant WTP-estimate in the end.
In the respondent group representing the general population, average numbers, retrieved from the patient-groups' responses, could then be used for the fixed comparator.

The scenario representing the genetic test is defined as reductions in number of medicine-shifts. Relative reduction would exclude bias related to the initial level in the fixed comparator, but it would give problems as the attribute is not a numerical one and cannot take on value of 2½, 1½ etc. Instead

absolute reductions could be used, for example 1 or 2 shifts less than without the test. This does however also pose challenges as some respondents might only have had 1 shift and even fewer, none at all.

The last issue has been how to model expected reductions in waiting time before an effect and a reasonable level of adverse side-effects is obtained. It seems likely that patients would be able to relate to this, if it was stated as one attribute with waiting time before the pharmaceutical and dosage for this, which resulted in an acceptable effect and an acceptable level of side-effects, were found. It is however not unlikely that time with dosage adjustments due to side-effects is less important than waiting time for alleviation of symptoms. And it is also not unlikely that reductions in waiting time for the last-mentioned will be larger than for the first one. This has resulted in the division of an attribute on waiting time into two attributes – one on each of the two time periods. This is supported by clinical practice, as the first objective will always be to relieve the patient of the depressive symptoms and thereafter try and adjust for adverse side-effects and try to reduce these.

As already discussed the focus group interviews also indicated that specialization, good information and certainty of having the best treatment possible matters to patients. But as explained, additional attributes on these matters will not be included. Primarily because it is not certain that the genetic test will affect specialization or information and because the test it self would imply a larger extent of certainty of having the best treatment possible.
Table 4 illustrates the attributes and levels for these that have been found to be of importance.

Table 4: Attributes and levels for a DCE on preferences for genetic screening.

Attributes	Levels
Number of shifts of pharmaceutical before an acceptable level of side-effects and effect is found:	Reduction of 1 or 2 shifts (As stated the number and ranges of the levels remains to be solved)
Time-period with pharmaceutical treatment but with symptoms (e.g. time before the treatment works).	Reduction of 1 or 2 months
Time-period without symptoms but with adverse side-effects bothering enough to continue regulation of dosage or consider shift of pharmaceutical.	Reduction of 1 or 2 months
Costs	D.kr. 200 (~ £ 18) D.kr. 500 (~ £ 45) D.kr. 1.200 (~ £ 110) D.kr. 1.800 (~ £ 160) D.kr. 3.600 (~ £ 320) D.kr. 6.000 (~ £ 540) D.kr. 12.000 (~ £ 1070) D.kr. 20.000 (~ £ 1800)

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Appendix: Translated interview guide

1. Opening questions – to make sure everybody gets to say something about some simple questions that can be replied in ½-1 minute.
What is your name? Where are you from? When was the first time you were diagnosed with a depression?

2. Introductory question – introduces the topic of the discussion and get people started thinking about their connection with the topic.
What is the first thing that comes to your mind when I say antidepressant treatment?

3. Transition questions – is supposed to move the conversation into the key question that drive the study. Resembles the purpose of the question above, it is just more specific.
If I ask you to think about the first time you became aware that you had such a serious depression that you needed treatment for it, how is your overall recollection of starting to take antidepressants and the process revolving this?
Try to think back about five good experiences from this?
Try to think about five bad experiences from this?

4. Key questions – allowing for long answers.
Does it matter when or if you have to wait for a treatment response to occur? And why?
How much does it matter that you have to accept the adverse side-effects of your medical treatment?
What is your general opinion about the use of genetic tests and genetic screening?

5. Closing.
What will happen next? Explain in more detail what the results will be used for etc.

6. Summation.
Did I get everything right? Do you have any suggestions for further interviews, or ideas for improvements?

Studies in Health Economics present the results of health economics research at Institute for Public Health, Health Economics, University of Southern Denmark.

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