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Perspectives on decision making in hematopoietic stem cell transplantation

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Chapter 01

General introduction

Hematopoietic stem cell transplantation; benefits and risks

Hematopoietic stem cell transplantation (HSCT) is an established, curative treatment option for patients with a hematologic disease, inborn error of immunity or metabolism, or bone marrow failure syndrome[1,2]. HSCT is a therapeutic option for an increasing group of patients. An HSCT involves the transplantation of donor hematopoietic stem cells. These hematopoietic stem cells are derived from the patient (autologous) or a healthy donor (allogeneic), either related or non-related. The most suitable, matched, and available donor will be chosen. The first choice is a human leukocyte antigen (HLA) identical related donor. HLA is an important recognition marker used by T cells to recognize self and not self. The better the HLA of the patients matches the HLA of the donor, the lower the risk that donor T-cells will not accept the patient's HLA. HLA is inherited from both parents, and thus, siblings might have identical HLA to the patient. However, unrelated donors sometimes have HLA that matches the patient's HLA sufficiently for mutual acceptance. Due to high-resolution HLA typing it has become possible to identify a matched unrelated donor (MUD) with increasing accuracy. Today, this allows for comparable HSCT results compared to matched HLA-identical siblings[1,3]. More recent developments in graft manipulation and graft-versus-host disease (GvHD) prophylaxis in HLA mismatched unrelated and haploidentical donors have resulted in increasingly improved outcomes. These developments include ex-vivo graft manipulation and in vivo T-cell depletion using posttransplant cyclophosphamide[5,6]. Consequently, this progress has led to an increased availability of donors, resulting in an enlarged number of this type of HSCT's[2]. On an annual basis, over 43.000 patients receive an HSCT in Europe, including more than 5.400 pediatric patients[4]. Of the pediatric patients, about 75% undergo allogeneic HSCT with as main indications about 14% acute myeloid leukemia (AML), about 27% acute lymphoblastic leukemia (ALL), and about 46% non-oncological diseases of which 37% primary immunodeficiency (PID)[4]. To be able to replace the hematopoiesis, to reduce the risk of graft versus host diseases, and graft rejection, patients undergo a conditioning regimen. The conditioning regimen involves the administration of myeloablative and immune-ablative agents, immunosuppressive antibodies, and irradiation. Following the stem cell

infusion, the donor stem cells will engraft, starting with the neutrophils and platelets in about two to three weeks. The recovery of the full immune system takes months and sometimes even longer. Up to about two years post-HSCT, regular medical follow-up is needed, focused on disease control, and controlling engraftment, GvHD, and chimerism. Thereafter, follow-up is meant to observe long term outcome, late effects, toxicity, and overall quality of life. Survival rates range widely based on the initial disease and transplant modality. In pediatric patients with AML the overall survival (OS) improved the last decades to 70-75% and the event-free survival (EFS) to 60-65%[7]. For patients with ALL the 2-year OS is about 75-91% and the 2-year EFS about 58-86% depending on risk profile, donor type and conditioning[8]. For patients with PID undergoing HSCT, survival is generally over 80[9,10].

Notwithstanding its therapeutic benefits, HSCT is an intensive medical procedure associated with various potential risks. These risks include the possibility of a fatal outcome related to multiple factors such as primary disease, performance score prior to transplant, patient age, and donor type[11]. HSCT-related risks can be divided into different groups. Firstly, the chemotherapy may induce several, primarily transient, short-term side effects such as nausea, vomiting, mucositis, diarrhea, alopecia, pain, skin problems, fatigue, hemorrhage, and hepatic complications. Secondly, following the conditioning regimen, there is a period of severe immune incompetence with a severe risk of infections. Infections may include bacterial, viral, or fungal infections that need close monitoring, prevention, and adequate treatment[12]. Thirdly, other short-term complications might arise during the engraftment phase, such as graft failure, graft rejection, and acute GvHD. Graft failure refers to the lack of donor engraftment or the loss of donor cells after initial engraftment[13,14]. One of the most challenging complications following HSCT is GvHD, and it is related to a significant risk of morbidity and mortality. Basically, GvHD is a response of the donor immune cells against the host tissue because of the histocompatibility difference between recipient and donor. Donor T cells may attack the patient's skin, gut, eyes, liver, or lungs. Symptoms may range from mild to severe to life-threatening. Acute GvHD often manifests in the first months post-HSCT. Treatment comprises a wide range of immunosuppression, which in turn raises the risk for infectious complications. Many treatment decisions are focused on the prevention of

GvHD, such as donor choice, conditioning regimen, in-and ex vivo T-cell depletion, and prophylactic medication[15,16]. Chronic GvHD manifests usually between three months and one-year post-HSCT. This chronic multi-system disease is characterized by inflammation and immune dysregulation, often resulting in impaired organ function[17,18]. Chronic GvHD may involve the ocular, oral, esophageal, skin, joint, fascial, and genital tissues[18]. Fourthly, a broad range of late effects post HSCT may occur and demand early detection and close monitoring. These late effects may include disease- or treatment-related complications such as iron overload, neurocognitive problems, pulmonary complications, endocrine disorders, infertility, renal complications, or psycho-social difficulties[19-21]. Insight into patient-reported outcomes post-HSCT not only supports early detection and treatment of late effects but also generates a broader understanding on the cohort level, supporting pre-HSCT counseling and decision making[22,23]. Despite improved HSCT outcomes over the last decades, a number of pediatric patients still die after an HSCT because of the recurrence of the initial disease or HSCT complications. The HSCT also impacts the patient's mental health. In survivors of pediatric allogeneic HSCT, anxiety- and depression rates were higher than those of children treated for health conditions without HSCT[24]. Health-related quality of life has been reported within normal levels; however, this was also reported worse for subgroups in patients with leukemia[24]. For families, the HSCT is an impactful event causing distress during and shortly post-HSCT, and even in the long-term[25,26]. Therefore, decision making for HSCT demands a careful decision-making process while balancing its benefits and risks before opting for an HSCT.

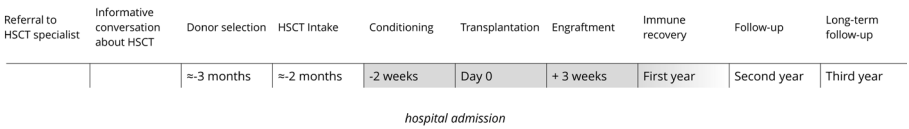

FIGURE 1.1 - Overview of the decision-making process and HSCT process.
Abbreviation: HSCT = hematopoietic stem cell transplantation.

(Shared) decision making in healthcare

In medical decision making, two types of decisions have been described[27]. The first type, the so-called "*effective decisions*", points to decisions in which scientific certainty exists, and clearly more pros than cons are known. Examples include antibiotics for infections in neutropenic patients and red blood cell transfusions in anemic patients. The second type, "*preference-sensitive decisions*", include decisions where no clear-cut answers are available, and the pros and cons depend on individual values. Examples are palliative care in considering (symptom) treatment and pain management in chronic conditions. Shared decision making (SDM) is an appropriate model to involve patients in thinking along with the healthcare professional (HCP) about, but not limited to, preference-sensitive decisions[28,29]. The SDM process consists of four steps, as described by Stiggelbout[29]. Firstly, the HCP clarifies that a decision has to be made in which the patient's opinion is important. Secondly, information is given about the available options with their advantages and disadvantages. Next, the patient's preferences will be explored, and the last step focuses on making the decision. Decision aids can support the SDM process, and its use results in patients feeling more knowledgeable, better informed, clearer about values, and probably have a more active role in decision making and more accurate risk perceptions when compared to usual care[30]. The use of SDM tools in pediatrics was shown to have a positive effect on the level of participation and knowledge in treatment decision making, and decreased decision conflict. The latter is associated with higher satisfaction among involved stakeholders[31,32].

In pediatrics, parents[1] mostly make decisions on behalf of their children. The involvement of the child in decision making, depends on age. In the Netherlands, children are legally allowed to make their own decisions from the age of sixteen. In the age range of twelve to sixteen years, teenagers may decide together with their parents, and for children below twelve years of age, parents decide for their children[33]. Pediatric patients of all ages need to be informed in a for them appropriate way. Next to these legally determined demarcations, it is also known that minors around the age of 12 are generally able to decide on medical issues based on age-specific capacities for decision making[34-36]. The extent to which

[1] When parents are mentioned, one can also read caregivers or legal guardians

children are able to be involved in decision making may vary based on the decision, their disease trajectory, competence, (mental) developmental stage, and age. The child's contribution to decision making and the degree of involvement should be considered based on their specific situation, while acknowledging the responsibility of the parent and providing the possibility for the child to participate in decision making[37]. Since 2020, SDM has been governed by the Dutch Medical Treatment Contracts Act (WGBO) in the Netherlands. In addition to the duty to inform, timely consultation with the patient about the possibility of refraining treatment, other possible tests and treatments by other HCPs, the time frame for carrying out the treatment, and its expected duration should be addressed. The caregiver should inform herself/himself of the patient's situation and needs and invite the patient to ask questions[38,39].

Being involved in treatment decisions is based on fundamental ethical principles of self-determination and autonomy[40]. These principles are especially important in preference-sensitive decisions because the patients' best interest in these types of decisions is based on the preferences of the patient in the specific situation. After all, clear evidence to choose one of the available options is lacking. In pediatrics, the HCP has not only to deal with the obligation to act in the child's medical best interest but also with the parental responsibility and authority in decision making about the life and health of a child. Moreover, the developing capacity for self-determination of a child must be included as already mentioned[41]. For preference-sensitive decisions, this includes that the preferences of the parent and/or the child, should be explored regarding the available options with the child's best interest in mind. On the contrary, in effective decisions, the child's best interest should primarily be considered through the evidence of the available options, where benefits outweigh the harms. The parental authority in these situations is limited in case of evident health benefits and is based on the right to protect and promote the health of the child. Whether and in which situations HSCT decision making is an effective or preference-sensitive decision seems to matter for the process of decision making.

HSCT decision making

HSCT decision making in pediatric patients with an oncological or acute non-oncological disease is a complex but often an evidence-based step in the protocol. In this protocolized step, families are mostly recommended by the physician to pursue HSCT, and parents describe this step mainly as 'agreeing to a plan'[42,43]. Therefore, HSCT decision making in these situations could be described as following all possible opportunities for curation and as an effective decision. However, decision making for most patients with non-oncological diseases is different. In particular diseases, like patients with a hemoglobinopathy or forms of non-acute life-threatening inherited immune deficiencies, the choice exists between conservative treatment or the HSCT. In these cases, HSCT can be considered as elective therapy and the decision approached as preference sensitive. The urgency and, thereby, timing are different. For patients with an oncological and acute non-oncological disease, time is often running out, and HSCT is the only chance for survival. In patients with a non-acute, non-oncological disease, HSCT can be scheduled and be chosen over conservative treatment. HSCT offers a viable option for curation with a prolonged life expectancy, less disease-related morbidity, and a better quality of life. This possibility for a plannable HSCT creates more time for more information about and preparing for HSCT[43].

Hemoglobinopathy and the possibility of a cure

A patient category that can benefit from an HSCT is patients with a hemoglobinopathy. Hemoglobinopathies, including transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD), are common genetic diseases affecting humans worldwide. It is estimated that worldwide 40.000 infants with TDT and around 300.000 with SCD are born on an annual basis[44,45]. Thalassemia is most common among the population in Middle East and Mediterranean countries and SCD among people of African origin. Due to immigration, increasing numbers of people with TDT and SCD are seen in other parts of the world, including the Netherlands. Regular red blood cell transfusions characterize standard care of patients with TDT because of chronic anemia, with

the risks of iron overload and allo-immunization. Due to developments in chelation therapy and the safety of blood transfusions, the life expectancy and quality of life for patients with TDT have increased over the past 20 years[46]. Nevertheless, TDT is still a chronic disabling disease with a serious impact on the daily functioning of patients and severe risks related to frequent transfusions. Supportive care for patients with SCD requires strict adherence to medication and lifestyle. These patients must deal with painful vaso-occlusive crises, cumulative organ damage, and anemia. A part of the patients need frequent transfusions or exchange of red blood cells with possible iron chelation therapy. SCD shows an interindividual variability in clinical disease manifestations and it is difficult to predict the course and severity of the disease over time. Both diseases are progressive and invalidating, demanding lifelong adherence to treatment and severely affecting quality of life and life expectancy[44,47].

At present, HSCT is the only established and widely available curative therapy option for patients with TDT and SCD[48]. The indication for an HSCT in patients with TDT is currently accepted as standard clinical practice because of the life-long transfusion need with associated iron accumulation and organ damage. Survival rates post-HSCT differ between about 85-95%, depending on the used donor, stem cell source, age at transplant, and other variables[44,48-51]. Besides, HSCT is developing over time with the increased use of alternative donors and related improved outcomes, chelation therapy has improved over the years, and gene therapy is developing[44,52]. The prognostic criteria for TDT show a homogenous pattern, which is not true for SCD. Patients with SCD show a wide genotypical and unpredictable phenotypical variation. Considering HSCT in patients with SCD is more of a deliberation between several factors. Guidelines describe for which patients an HSCT is indicated based on SCD complications, age, donor availability, and center experience, and in clinical practice, more factors seem to influence the indication[48]. Local practices vary, but the field of HSCT for patients with SCD is developing, based on gained knowledge and experience and the developments in HSCT. In recent years, increasingly adult patients with SCD have been transplanted with non-myeloablative conditioning in the case of HLA-identical donors, but also with the use of haplo donors[53,54]. Moreover, gene therapy for patients with SCD is emerging as a promising future alternative, but as for TDT, its currently limited accessibility still hampers its

widespread clinical use[55,56]. HSCT survival rates for patients with SCD ranged between about 88-93% depending on the chosen donor and age at HSCT[55,57,58]. A recent EBMT-registry study showed a two-year overall survival of 99% in a cohort of pediatric patients with SCD transplanted with a matched sibling donor[59].

The difficulty of HSCT decision making for patients with a hemoglobinopathy

During their treatment trajectory, children, young adults, and caregivers with TDT or SCD may be offered the possibility of the continuation of supportive non-curative treatment and HSCT. The timing of facing this option varies from early in the illness process, shortly after the results of the newborn screening, to somewhere during adulthood by, for example, information on social media. There is no clear consensus among HCPs worldwide about transplanting patients with a hemoglobinopathy especially SCD patients[60,61]. A multi-center survey studying HCP's approaches showed nevertheless that most were enthusiastic about HSCT for SCD and refer children for HSCT[62]. In a qualitative study on physicians' perspectives on SCD treatment options and decision making, two narrative approaches were identified[63]. Firstly, a collaborative approach was identified, where professionals emphasize the need to discuss all treatment possibilities in order to provide sufficient information to make an informed decision. Secondly, a proponent approach was found, strongly advocating a pre-determined treatment plan and providing patients and families with information, with the goal of convincing them to accept this treatment. Physicians' attitudes on therapy options, decision making and consequently their approach was influenced by patient-related, disease-related and physician-related factors, and also by institutional frameworks[63].

When focusing on the attitudes of families and patients with hemoglobinopathies, there is diversity in how HSCT is perceived, which might change over time as the treatment improves. Less than half of the parents in a hypothetical situation or in a retrospective medical records analysis choose to move forward with HSCT[64-66]. The main reasons to waive the HSCT procedure were lack of an HLA identical donor; lack of time, resources or support for the

procedure; belief in continuation of transfusion therapy; fear of SCT-related risks; and preferences for future hydroxy-urea-based options[66]. Somehow contrasting were the results of a reference gamble paradigm survey where the majority of the parents and patients, but not all, indicated they were willing to accept a certain level of the HSCT risks of mortality, GvHD, or infertility[67]. Until several years ago, while the research reported in this thesis was initiated, little (prospective) evidence was available on how SDM was introduced in this field and the perspectives of patients and caregivers actually considering and undergoing HSCT. More qualitative research on perspectives regarding HSCT decision making in patients with hemoglobinopathies, mainly SCD, was published in the last couple of years. Qualitative data showed that for families of patients with a non-oncological disease that proceed with HSCT 'desiring a more normal and better quality of life' was important, as well as 'worrying about disease progression and losing the window of HSCT opportunity'[68]. An American research group performed some qualitative studies last years on the perspectives of patients with SCD and caregivers while considering HSCT. A retrospective qualitative study about patients' and caregivers' HSCT decision making showed the following influencing factors: the burden of sickle cell disease, education received from HSCT physicians, family influence, and the availability of an HLA-identical sibling donor[69]. The three most common concerns brought up by participants were morbidities associated with HSCT, social isolation, and impact on family dynamics. For families, the HSCT changed a hindered childhood into a disease-free life with the possibility for a 'new life'[69]. Another qualitative study described the results of caregivers' considerations while having had a consultation about HSCT for their child with SCD. Results revealed their motives for curation, and how caregivers learned about curative options by social networks and media. These motives included the limitations for their child caused by the disease or concerns regarding future impact. Gene therapy, although not yet available as a regular treatment, was considered a less complicated and harmful treatment[70]. Qualitative data reporting the perspectives toward HSCT of adult patients with SCD and caregivers of patients with SCD also showed the informational need for HSCT and described decisional dilemmas regarding HSCT for patients with SCD[71]. The latter was confirmed in another study, where families considering HSCT for pediatric patients with SCD experienced varying levels and sources of decisional conflict[72].

The possibility of curation is promising for patients having a disease that unfavorably affects quality of life and is associated with a limited life expectancy. The non-acute indication for HSCT and the potential HSCT risks complicate the choice of an HSCT as a potential curative therapy for patients with a hemoglobinopathy. Considering these no-clear-cut answers on the best standard of care, patients' perspectives should play an important role in decision making. Most research up till now has been retrospective in nature. To achieve an SDM process, more insight is needed into the current prospective process of decision making, the experiences, and considerations of potential Dutch HSCT candidates, their parents, and HCPs.

Aims

The aim of this thesis is to enrich the existing knowledge on decision making for pediatric patients with in-depth insights into the perspectives of patients, caregivers, and healthcare professionals considering an HSCT in circumstances in which there is no clear-cut answer on what the best option for the individual patient is.

More specifically, we aim:

- To prospectively analyze the decision-making process for children and young adults with a hemoglobinopathy and/or their caregivers deciding on HSCT;
- To explore experiences of and identify the considerations on HSCT decision making for patients with a hemoglobinopathy from the perspectives of involved health care professionals;
- To explore experiences of and identify the considerations HSCT decision making for patients with a hemoglobinopathy from the perspectives of children, young adults, and caregivers.
- To identify how patients' and families' values can be involved in decision making for HSCT in patients with a hemoglobinopathy.

Methodology: Qualitative research

To gain insight into the experiences and considerations of involved stakeholders in HSCT decision making a qualitative approach was used. A qualitative approach

allows for a deep understanding of human behavior and experiences. Intrinsic considerations and meanings regarding the subject of study can be explored. Qualitative data will describe the meaning of the perspectives being studied. Where in a biomedical setting previously mainly quantitative research was valued as the standard, nowadays qualitative research shows its value by adding an inner perspective of the participants. In qualitative research, the researcher is its own instrument, demanding the responsibility to control rigor and reflexivity. This can be controlled by data triangulation, researcher triangulation, writing memos, and a careful process of obtaining, processing, and analyzing the data[73]. Qualitative research is a constantly developing field, and as quantitative research, qualitative research should comply with quality rules. Quality standards for reporting qualitative research, like the COREQ or SRQR, are being requested by more and more journals for transparency reasons[74,75]. In this thesis, the COREQ checklist is used to report the qualitative studies.

This thesis used interviews (Chapter 2, 4, and 6) to gain a deeper understanding of the perspectives of patients, caregivers, and HCPs regarding HSCT decision making. Semi-structured interviews were conducted by the author of this thesis, experienced in qualitative interviewing. Semi-structured interviews provide the opportunity to gain insight into the respondents' considerations, whereas, at the same time, the focus of the interview can be controlled. Participants were recruited by the local staff of the participating centers. Interviews were held at a setting of the respondent's preference, often their home. The interviewer explained that individual interviews were preferred to hear the personal perspective of the respondents, but ultimately, it was left to the preferences of the respondents, leading to different interview composites, like with other family members. If necessary, a professional interpreter was asked to translate the conversation (Chapter 6). Topic lists were used as interview guides to ensure that all topics were covered to answer the research questions. These topic lists were based on the literature and the research team's experiences. Based on insights from the interviews and analyses, topic lists were evaluated and adjusted throughout the project. Interviews consist of open-ended questions intended to welcome the respondent to share their perspectives. Data collection in Chapter 2 and 4 had a cross-sectional character, whereas the studies reported in Chapter 3 and 6 had a longitudinal character, as shown in Table 1.1. Repeated interviews

were used in Chapter 6 during the decision-making process to better understand the actual decision-making process. All interviews were audio-recorded and transcribed verbatim. Following each interview, observational memos were written to describe the setting, atmosphere, circumstances, and the researcher's reflections on the interview themes. Furthermore, during the process, theoretical memos were written with thoughts, interpretations, and ideas regarding the analysis and further needed data collection. Memos were used during the analysis process as a reminder of interactions and as part of the thinking process[73].

Inductive thematic analysis was used to identify patterns and themes that reflected the respondents' perspectives[76]. The data collection and analysis process had an iterative character, moving back and forth from collection to analysis and back again while themes were developing. No new respondents were enrolled in the study when on a conceptual level no new input on the theme descriptions was found in the interviews or when the information power was valued as adequate, related to the study aim, sample and gained knowledge[76,77]. Transcripts were thoroughly read for familiarization with the data, followed by the coding process. The coding process started with open coding, which was conducted independently by one or two team members. Codes and themes were discussed among the team members until consensus was reached. At the stage of open coding, the transcripts were segmented into meaningful parts and labeled (coded) with a description of the essence of that part of the text while staying close to the respondents' words. During the next stage, focused coding was used, comparing codes and categorizing the developing codes more conceptually. As a last step, categories were described into themes, interpreting the data and describing the meaning of the categories. Within this process of defining and describing themes, discussions within the research team provided important input in interpreting and describing the meaning of the themes[78]. The research team was involved in all phases of data collection and analysis to enhance validity and credibility[76]. Coding was supported by qualitative data analysis software NVIVO10 (Chapter 2) and ATLAS.ti (Chapter 4 and 6).

Outline

Chapter 2 describes parental experiences with end-of-life decision making in allogeneic pediatric HSCT. Although being a different patient group, it gives valuable insights in the HSCT decision-making process. **Chapter 3** presents to which extent a shared decision making approach is used in conversations between healthcare professionals and patients with a hemoglobinopathy and/or their caregivers considering HSCT. The perspectives of healthcare professionals on HSCT decision making for patients with a hemoglobinopathy in the Dutch population are described in **Chapter 4,** whereas those of an international group are outlined in **Chapter 5. Chapter 6** describes the HSCT decision-making considerations and experiences of children and young adults with a hemoglobinopathy and of their caregivers. This thesis ends with discussing the main concepts in HSCT decision making in **Chapter 7,** where we also reflect on future perspectives and the methodology used.

TABLE 1.1 - Conversations and interviews throughout the decision-making process.

	Consul-tation with referring HCP	Consul-tation with HSCT specialist	Interview pre-decision	Interview around decision	HSCT	Interview during HSCT	Interview post HSCT/post decision	Months between first and last interview	Months between HSCT and last interview
Case 1	P+M+F	P+M	P+M M+F	P M	N	N/A	M	24	N/A
Case 2		F+M		M+F	N	N/A	M	23	N/A
Case 3		P+M+F P+M+F		P+M+F	Y	M+F p	P+F	26	14
Case 4	N/A	P+M+F		M	Y	P	M	12	12
Case 5		M+F (P+)M+F		M F	Y	P	P M	20	12
Case 6		M+F M+F	M+F		Y		M+F	17	-16
Case 7		P+M+F M+F	M+F		N	N/A	M F	19	N/A
Case 8	M+F	P+M+F	P+M+F	P+M	Y	P+M	P+M	23	11
Case 9	N/A	M M+F			Y	M	M	19	18
Case 10	M+F	M+F	M F		N	N/A	M+F	17	N/A
Case 11		P P		P	Y	P	P	20	17
Case 12		P+M+F		P+M	Y	P+M	P+M	20	18
Case 13				M	Y			x	-47
Case 14		P+M+F			Y	P F	P F	21	21
Case 15		P		P	Y	P	P	19	14
Case 16		P		P	Y	P	P	19	10
Case 17		M+F M+F		M+F	Y	M+F	M+F	19	16
Case 18	P+M	P+M+F	M		N	N/A		x	N/A
Case 19*		M+F	M+F		N	N/A		18	N/A
Case 20	N/A	M+F		M+F P	Y	P F	P M+F	18	13
Case 21		M M		M	Y	M		6	1
Case 22*		M+F M+F			Y	M	M F	18	10
Case 23		P+M+F		P+M+F	Y	(P+)M	P+M+F	13	12
Case 24		M+F			Y	M	M	6	6
Case 25	P	P		P	Y	P		8	3
Case 26		P+M		P+M	Y	P+M		14	3
Case 27	P		P	P	Y			6	≈-10

**One family.*
Abbreviations: Y = Yes; N = No; P = Patient; M = Mother; F = Father; + = shared interview; Other relatives taking part in the conversations are not included in this table since they were not officially study participants.

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