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# **Pediatric cancer families' participation in whole genome sequencing research in Denmark: parent perspectives**

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## **ABSTRACT**

With an impending introduction of genome sequencing into pediatric oncology to facilitate personalized medicine, this study examines parent perspectives on participating in Whole Genome Sequencing (WGS) research in the difficult weeks following diagnosis.

As an embedded part of STAGING, a project aiming to implement WGS of all newly diagnosed pediatric cancer patients in Denmark, a parent perspective study (PPS) was conducted by a clinical geneticist and anthropologist to document pragmatic, social and ethical dilemmas. Following genetic counselling, systematic debriefings were held and the anthropologist carried out in-depth parent interviews (N=30 parents to 15 patients).

Parents were approached about STAGING 2-28 days after diagnosis. The majority of interviewed parents reported that an early approach had been feasible for them, a few found it too early. Participation was explained in terms of altruism and a desire to learn more about why their child had developed cancer. A number of parents openly disagreed about the amount of information they wanted reported back.

Enrollment in WGS research around the time of diagnosis is feasible, however flexibility from researchers is essential. Notwithstanding high participation rates and a tendency to choose full disclosure, caution as regards the consequences of participating in WGS research is warranted.

*Key words:* whole genome sequencing, pediatric cancer, parent perspectives, ethics.

## **Introduction:**

The time following a pediatric cancer diagnosis is both turbulent and distressing for the child and family. The diagnostic process requires numerous tests in the form of imaging, blood tests and biopsies. Parents and family members question why cancer has befallen their child and are anxious to learn about treatment options and in particular their child's prognosis. As many a parent has described it in this and other studies (Woodgate & Yanofsky, 2010, and Liaschenko & Underwood, 2001), learning that your child is suffering from a potentially life-threatening disease can be surreal:

I felt like... it was like I was living in a bell jar. I mean, you're just really sitting and waiting for time to pass. It's a strange feeling. (Patient 10, Father)

So, you still wake up, especially in the beginning, you wake up in the morning and think 'this nightmare needs to end, I'm going to wake up now and it will be gone'. But it isn't... It's like the opposite of waking up from a nightmare since you wake up to a nightmare. (Patient 14, Mother)

At the same time, especially if parents have gone through a prolonged period of uncertainty filled with increasingly frustrating visits to the family doctor and local hospitals as various examinations and tests are carried out, a confirmed diagnosis can also come as a relief:

We came in for our consultation with [treating physician] at 10 o'clock on the Thursday and that was really comfortable. I mean, even though we got the worst possible news you could conceive of, it was a relief in some way... In a very twisted sort of way it was a huge relief. Because, well, now there's a plan, yes, somebody is going to do something. (Patient 15, Mother)

It was a senior doctor and a couple of nurses who gave us the diagnosis. They had ascertained that [daughter's tumor] was localized... they had checked her lungs and looked at all the other bones. Her whole body had been scanned, you see. And there is nothing anywhere else. So that's what they call a localized tumor. They know where it is and seem to be on top of things... If it's at all possible to feel relief, I did. (Patient 14, Father)

Cancer treatments are notoriously taxing on patients causing them discomfort which in turn generates substantial worries and distress for parents and loved ones. During this time, parents receive complex information about test results, the nature of their child's cancer, possible treatments, side effects and potential sequelae related to the disease and treatment. Many families will be able to go home soon after diagnosis, returning periodically for ambulatory treatments and examinations. Others will be hospitalized for days or weeks because of treatment-related complications or disease progression. At the same time, many childhood cancer patients have siblings who must also be cared for and whose daily routines of school and social activities need to be maintained as best possible, often with the support of grandparents, other family members and friends.

It is in the midst of such turmoil that pediatric cancer families are asked to participate in medical research, a good part of which is treatment related although some non-treatment related studies are introduced to families on the day of diagnosis since securing pre-treatment biological samples is vital for the interpretation of their results. Parents are often overwhelmed and disoriented in the time following a diagnosis which makes processing information for them a challenge (Woodgate & Yanofsky, 2010, and Scollon et al., 2014). Moreover, parents are entirely focused on the treatment

and care of their child and hence on shielding them from any unnecessary burdens at a time when they are experiencing discomfort from treatment and the cancer itself (Dekking et al., 2015). These circumstances raise important questions about whether and if so, how meaningful informed consent can be achieved as well as how families can be supported in their decision making.

Since January 2017, all pediatric cancer families in Denmark have been asked if they would be willing to participate in WGS research in the weeks following diagnosis with the long-term goal of furthering precision in the treatment of pediatric cancer. Although genomic sequencing is not currently routine in pediatric oncology, a few studies have recently introduced WGS and/or whole exome sequencing (WES) to families of newly diagnosed pediatric cancer patients, not least in anticipation of sequencing's transition from laboratory to clinic (Zhang et al., 2015, and Parsons et al., 2016). Further to meaningful informed consent and decision making, WGS research with newly diagnosed childhood cancer patients also raises a set of ethical and social challenges around potential long-term consequences arising from findings (primary or secondary), potential involvement of other family members, children's right to an open future, data security and privacy, the establishing of biobanks for future research and the potential implications of important future knowledge for patients who have donated DNA to a biobank (Johnson et al., 2017).

In this study we explore parent perspectives on participating in WGS research specifically in the weeks following diagnosis of pediatric cancer. The study was carried out as an embedded part of the Sequencing Tumor and Germline DNA – Implications and National Guidelines (STAGING) project, which – to our knowledge – is the first of its kind to prospectively offer WGS to a nationwide cohort of newly diagnosed pediatric cancer patients. Early introduction of WGS is necessary in order to allow for treatment adaptation (e.g. alterations in radiation doses) and prevention of toxicities. While existing studies have focused on pediatric cancer families' expectations and attitudes towards WGS (McCullough et al., 2016, Oberg et al., 2015 and Anderson et al., 2017). The objective of STAGING's parent perspectives study (PPS) was to document pragmatic, social and ethical dilemmas related to *the actual process of participating in* research involving genetic counselling and WGS of newly diagnosed childhood cancer patients as described by parents.

### **Setting:**

In Denmark, pediatric cancer patients are treated at one of four treatment centers - located in Copenhagen, Odense, Aarhus, and Aalborg. Families of all newly diagnosed pediatric cancer patients aged 0-17.9 are asked whether they would consent to participate in the STAGING project, as are families of patients diagnosed with Langerhans Cell Histiocytosis (LCH), Myelodysplastic Syndrome and patients with cancer relapse more than 6 years after their primary diagnosis. Following agreement with treating physicians, research nurses in the four centers approach families concerning project participation within the first month from diagnosis and provide them with a short oral presentation as well as written information. A genetic counselling session is scheduled with those families who agree to hear more about STAGING. During this session, families are informed of the different parts of STAGING, their family pedigree is mapped and families are informed about different options when it comes to choosing what they would like reported following their child's WGS. Families can choose to have information on 1) disease-causing findings in cancer predisposition genes and disease-causing incidental findings, 2) disease-causing findings in cancer

predisposition genes, or 3) no information on findings from the WGS. For the latter two options families are informed that there may be findings with potentially severe health consequences for the child or parents, including early death, which may be reported to them nonetheless. Examples of such findings are given during the consultation. On the basis of this information families are asked to make a decision about STAGING participation, and which level of information they want reported back.

Counselling sessions are observed by an anthropologist, who during the session presents the PPS. If families agree an interview is set up. After genetic counselling the clinical geneticist and the anthropologist debrief regarding how they experienced contact to the family, main concerns or questions raised by the parents, and how much parents indicate that they want reported back to them and whether they agree on this (figure 1). The clinical geneticist providing the genetic counselling is the first author of this paper, and the anthropologist interviewing the families is the last author. The STAGING project including the qualitative study on which this paper is based was approved by the regional ethical committee (H-15016782) and the Danish data protection agency (j.nr.: 2012-58-0004, RH-2016-219, I-Suite no: 04804).

## **Methods:**

The participation rate in STAGING has been high (of the 80 approached families as of July 2017, 3 families have declined participation, 10 families have postponed their enrollment and 68 families have accepted participation). Embedded within STAGING, this study comprised anthropological observations of 15 genetic counselling sessions (with a total of 30 parents) (table 1), 15 systematic debriefings between the clinical geneticist and anthropologist and 17 in-depth interviews with parents (13 with both parents together and 4 with individual parents). Inclusion was based on convenience sampling since the PPS was optional for families participating in STAGING and organizing an interview with parents following genetic counselling was not always possible (despite them agreeing to be interviewed) because of their life circumstances. For this same reason, debriefings are based on the counselling sessions of 7 of the interviewed families and of an additional 8 families who were not interviewed after genetic counselling. The role of the anthropologist during counselling sessions was to observe the communication between clinical geneticist and parents, taking note of the mood during the conversation as well as any questions raised or comments made by parents during the session. Shortly after the conclusion of a genetic counselling session, the clinical geneticist and anthropologist reconvened to systematically document the quality of communication during the counselling session as well as any concerns or questions raised by parents (text box 1).

Interviews were carried out at a time and location that was most convenient for participating parents, most often in their homes but also in private consultation rooms on the pediatric oncology ward or in the family's private ward room. Whereas observations allowed for the documenting of unsolicited questions and concerns raised by parents during counselling sessions, interviews were carried out using a semi-structured interview guide covering 1) parents' accounts of the time leading up to and following diagnosis; 2) how parents' experienced being asked to participate in non-cancer-therapy research in the days and weeks following diagnosis; and 3) parents' views on

the potential consequences of participating in WGS research (text box 2). Interviews were audio-recorded and lasted between 50 and 70 minutes.

### **Analysis:**

Post-counselling debriefings were recorded in standardized forms. Interviews were transcribed verbatim by research assistants and quality controlled by the anthropologist. The resulting data set of 15 debriefing reports containing observations and notes and 17 transcribed interviews with a total of 30 parents forms the empirical basis of the analysis. We performed a thematic analysis of both debriefing reports and transcribed interviews in order to systematically code identifiable themes emerging out of parents' reactions to and reflections on participating in WGS research in the weeks following a pediatric cancer diagnosis (Boyatzis, 1998, and Fereday & Muir-Cochrane, 2006). Initial coding was based on the areas covered by the study (time leading up to and following diagnosis, being asked to participate in research during this time and potential consequences of participating in WGS research). This was done independently by the clinical geneticist and the anthropologist, after which analysis meetings were held to inductively agree on key themes emerging out of parents' perspectives on participation in WGS research. All quotes have been translated from Danish by the authors. Debriefings provide insights into parents' initial reactions to being asked to participate in WGS research whereas interviews provide insights into how parents' reason and reflect on both the circumstances surrounding them and their actual decision to participate. Hence, in this study, parent perspective refers both to the observable circumstances from within which parents are asked to participate in research as well as their reasoning about participating in WGS research.

### **Results:**

#### When is the right time?

With many ongoing research projects within the field of pediatric oncology in Denmark, it is not uncommon that families are asked to participate in several research projects. The number of projects differs between families, as patients with more frequent diagnoses are eligible for several projects, whereas others with rarer diagnoses are asked to participate in only one or a few projects. Indeed, at times, researchers are literally waiting their turn to speak with a family about research participation or to schedule an appointment to do so. As recounted by one mother "*well, there was that one day when it was just... there were kind of four or five researchers outside our door, right?*" (Patient 8). Similarly, the father of another child remembered how during the early days of hospitalization "*there were people coming in all the time, and [son] was feeling bad, as soon as one person left the room, another one trudged in, right? And then after we had just gotten him to sleep, another one came in 'Oh, is he sleeping?' 'Well, not anymore.'*" So, there was just a lot for us to process, right?" (Patient 4).

In such a research-intensive setting, interviewed parents' experiences of the timing of being approached about WGS research participation were individual. Among the 15 interviewed families, the first approach with written information about STAGING was made from 2 to 28\* days following diagnosis and genetic counselling took place from 7 to 42\* days following diagnosis

(\*90% range). The majority of interviewed families reported having had a good experience when approached about research and appreciated the patience and flexibility that researchers had shown them, although a few felt that approaches from researchers were too forthright. At the same time, no clear pattern emerged regarding when the right time to be approached might be, rather parents emphasized that this was highly individual. Among those parents who were interviewed, one couple clearly stated that they felt the approach had been too soon, just as a few others expressed that they appreciated not having been approached in the first week:

Father: Way too early actually, I have to say.

Mother: We had just learned that [son] had some kind of cancer, you know, we were in crisis, both of us, right? So, um, I can definitely remember that I was quite irritated about that. (Patient 13, written information on day 2, genetic counselling on day 42)

Well, I think for us the timing was fine, when you came, it wasn't the first time we were there [hospital]. So, that's the only thing I would imagine that... I think I would, as a minimum, wait until the second time that families are at the hospital for treatment. Because during the first stay, it *really* is ... it's chaotic and there's so much happening, I mean, I don't think that one can... there's not much you can take in at that point. (Patient 14, Father, written information on day 26, genetic counselling on day 27)

Other families had different explanations as to why they felt being approached shortly after hospitalization and diagnosis had worked for them:

Well, of course, it is somewhat difficult to deal with all the information, especially in the initial phase, during the first days, you're still in shock and, well you know, you can't really focus on anything other than what's going on with [daughter]. But on the other hand, I do think that one has to consent at that point if one wants to participate from the beginning, so um, I can't really see how it could be done otherwise, but it can be difficult to take in all of the information and really know what research projects we have said yes to. (Patient 1, Mother, written information on day 2, genetic counselling on day 3)

Yes, but at the same time it does help that you come and ask about the same thing many times, because you can't remember half of what you've been asked about. Then you get maybe 5% more, "oh yeah, now I do remember. But what was it that you asked me about?" Right? So it's very good that you come and ask about the different things. So... And that it could be spread out over... Yeah, I don't know... Maybe it should be spread out over a longer period. But, I know that's difficult if you need an answer or permission to take a sample in the early phase when they are doing that anyway, right? So, well yes, I think it's alright, I mean... They always approached us with a smile and would say "well, you just tell us if it's not the right time, we can come back". So it hasn't been like it had to be right now. And that's... that means a lot to us. (Patient 12, Mother, written information on day 4, genetic counselling on day 20)

Well, maybe it's... I don't think that we've been... We've been emotionally okay. I mean if you're really affected I think it would have been... it could be hard to take it all in, right? But I don't think we've been... [daughter] wasn't in very intensive treatment when you came in, right? So it's been fine for us, because I think we've been able to take it, we've felt that we were at a point where we could talk about such things. (Patient 5, Mother, written information on day 9, genetic counselling on day 9)

It was a good experience [being approached about the project], a very good experience. There's not much that has been good in 2017, but that was a very good experience. And there was no feeling of pressure or a sense that it was being forced at all. Not at all. And it doesn't matter when I see [researcher] at the hospital, she always waits until there's an appropriate time. (Patient 11, Mother, written information on day 24, genetic counselling on day 31)

When it comes to being approached about research participation, these parents highlight on the one hand, their emotional state, a sense of being overwhelmed and intensity of treatment as important factors, while on the other underlining how important flexibility and forbearance on the part of researchers was for them given their life circumstances.

“Why has this happened?”

Debriefings revealed that six out of fifteen couples had expressed a wish to make a contribution and help others without prompting, and similarly six couples stated that they wanted to learn more about the health of their child and/or family. During anthropological interviews parents were asked directly about their reasons for participating in research with virtually all participating families expressing a wish to help future families. Some interviewed parents also suggested that they felt a duty or obligation to participate in research or that they trusted the doctors who were involved in research. When it came to participating in WGS research specifically two themes in particular stood out. Firstly, most families reported having wondered why their child had gotten cancer. Parents had asked themselves, each other, and their child’s physician ‘why?’, with a number of families having been told by their treating physician that their child’s cancer was purely bad luck, and that hereditary causes of childhood cancer are extremely rare, if the notion was not dismissed altogether. Hence, some parents saw WGS as an opportunity to potentially get an answer to this question. As one mother recalled:

But it really is one of the fundamental things to figure out: why has this happened? Obviously, that is also a question he [son] has had himself – why me? Why did I get this? And we can’t give him an answer. Mm, it isn’t a given that we will get an answer through this, and we have told him that, but the opportunity to get some answers is present [in this study]. (Patient 9, Mother)

Other parents could not accept that no one could tell them why this had happened to their child, and had researched it themselves – through internet searches, soliciting second opinions, and more:

But I came across – while researching her diagnosis and whether there was something else that could be done – that it may be genetic, and that it may be the case in an overwhelming number of cases. As I read it, bear in mind it is difficult to interpret, but as I read it, there is a genetic mutation which arises, which isn’t inherited, but which occurs in 85% of [daughters tumor type]. (Patient 14, Mother)

Similarly, some parents had already prior to being approached about WGS wondered if their child’s disease could be due to genetic factors. Some of these families had knowledge of other genetic diseases running in the family, and had gone through genetic counselling and testing previously. Others wondered whether there was a connection to other cases of cancer in their wider families:

But one can say we are constantly being told that they don’t know a lot [about the cause]. And at one point I actually did ask [son’s doctor] – ‘Is this genetic? Is this something which can be inherited?’, because as it happens we do have quite a lot of family members who have had cancer. (Patient 6, Mother)

The question of ‘why’ often led to concerns for the affected child’s siblings; also prior to being approached about participation in WGS research. Parents expressed concern both for siblings’ welfare during such a tumultuous time, but also for siblings’ health and in particular their risk of cancer: *“It was one of the first things we asked them ‘what about the other children?’... There is a*



*brother and a half-brother... But we have continuously been told that there was no risk at all to them". (Patient 10, Mother)*

Closely linked to the concern for other siblings was the hope that through participation in WGS research, families would be prepared for another event in the affected child, siblings or parents. Overall, parents explained their participation in WGS research as driven by altruistic concerns and a wish to increase knowledge of their child's cancer and their family's own health risks.

### Making the right decision

Consenting to WGS research requires that parents consider the potential consequences of genome sequencing for their child, themselves and their families as well as what kind of information they would like to have reported back following WGS. As such, it is 'thought work' that is required of those families who consider participation in WGS research, a task which takes place through discussions and deliberations between mother and father at home around the kitchen table or during a quiet moment on the ward. And it is a task that is not always welcomed in the midst of a chaotic time in the early days following diagnosis. As put by one father (who was not interviewed for this study) during genetic counselling: "*We have so much that we have to consider right now, this is not something we need on top of everything else*". Similarly, a mother of another child recalled how "*I remember thinking that it was actually more difficult having to think about it [which findings to have reported back], than it was deciding to participate in the study, and I actually thought that if I have to figure out where I stand then I can't take part in this, because I just can't deal with it at this point*" (Mother, Patient 6).

Our analysis of parent interviews revealed two particular themes related to how parents deliberated on their participation in WGS research. Firstly, a number of parents who ended up opting for full disclosure described having pondered the tension between receiving findings that could help them prepare for the future while at the same time possibly introducing anxieties about that same future:

I'm wired in such a way that I want to know things, and if there is something that I need to take into consideration then I'll act accordingly, you could say. You could of course ask would it be better not to know and to go about one's life unaware until something happens all of a sudden. Maybe there is a case to be made for that, but in that case you wouldn't be able to plan your life accordingly, you could say. (Patient 11, Father)

You have to try to control your own web of thoughts, because I am certain that you can become quite nervous if you get to know that you have an increased risk for 4-5 diagnoses which are serious... We'll have to... None of us has ever tried that, right? So we'll have to try and... We'll have to see how we tackle it and it may well be that we end up concluding at some point that perhaps it would be better not to have known. But I just think that I would then end up fretting about what was in that genetic test that I didn't read about? What do they know that I don't know? (Patient 14, Mother)

A second theme was that of discordant views between parents. Although 14 out of the 15 interviewed families opted for full disclosure of WGS findings some parents openly discussed their different views during genetic counselling as well as follow up interviews. In discussing their views, parents often referred to the *kind* of person they or their partner was. During one of the observed counselling sessions, a husband and wife got into a heated exchange about the value of receiving findings in the form of a risk estimate. While the mother was convinced that getting as

much information as possible would be good, the father was concerned about possible over treatment on the basis of risk and in general that receiving such findings would result in them having to fret about their future. STAGING requires that parents are in agreement about what findings they would like to have reported back. And where some parents made a point of highlighting that they were similar to their partners – *“I think I’m similar to [husband] in that way, I’m also quite realistic when it comes to these kinds of things.”* (Patient 11) – other couples pointed out that *“In that way my husband and I are very different”* (Patient 8) which then required further deliberations at home before a final decision on which findings they would like to have reported back was made. Take this exchange between mother and father during their post-counselling interview:

Mother: We talked about it a lot at home, what we wanted to know, right?

Father: Yeah and well... I was probably more skeptical than you were.

Mother: Yeah you weren't as hooked as...

Father: But, well the thing is, what the hell is it we are going to find out?

Mother: Yeah, we did talk about that a lot. It was actually... I mean, you were kind of like, in the beginning, arghh you just had to kind of... You do also need time to think things over, right? I think it was about two weeks where we were thinking about it until we finally agreed that we would tick the box where you get to know everything.

Father: It's really about reactions, right? What if we get some negative findings? How will we react?

Mother: Yeah, then you have to...

Father: I mean, the way I see it, let's just live our lives while we can and enjoy, and I think...

Mother: I don't want to fret about getting some kind of cancer...

Father: No, I think... I mean, we all just want to go to bed at night and then not... when we get into our old age.

Mother: When we get old, right?

Father: Yeah. But that's just not how it is always. So it's just that, I mean also because, how much is it going to change our lives if we get some negative findings. That's really what I've been thinking about. (Patient 3)

In another interview, the mother and father began debating about what risk threshold was high enough to make a finding relevant. The father suggested that he would want to receive a finding if the variation's penetration was 70% or higher, to which the mother responded incredulously suggesting that anything above 20% was good to know.

High participation rates in and a tendency to opt for full disclosure suggests that a desire to know about possible genetic causes of their child's cancer and the possibility to act preventively trump concerns about how families will deal with WGS findings. But this does not mean that dilemmas are fully resolved, especially in cases where a mother and father are not in complete agreement but also in cases where individual parents are in two minds about which kind of findings they would like to have reported.

## **Discussion:**

### Timing of genetic counseling

Previous studies and the general consensus among health professionals within the field of clinical genetics largely recommend that genetic counseling and testing should not take place in the acute

phase of illness (Oberg et al., 2015). Only in cases where the results of genetic testing have implications for the choice of treatment is this recommendation foregone. A few studies have implemented genetic counseling around the time of diagnosis, as is done in this study, however, these studies have not examined how parents perceived being asked around the time of diagnosis (or at least did not report having done so) (Scollon et al., 2014, and McCullough et al., 2016). Oberg et al. conducted interviews with participants of two focus groups (one with parents/guardians of children with cancer and one with cancer-naïve participants) hypothetically asking both groups about the appropriate time for being approached about WGS and the resulting ability to make an informed decision about WGS (Oberg et al., 2015). They found that approach about WGS could be done early on, but that consent should be given following a two-step approach, where the first approach is at time of diagnosis to allow for securing of invaluable tumor material, while the second step involving counselling should not take place until 1-2 months after diagnosis in order to allow for families to come to terms with the diagnosis and initial shock. Among interviewed families in our study, we found that a large number of parents did not have objections to being approached or to receiving counselling within the first 4 weeks following diagnosis. This is interesting seen in the light of current recommendations in regards to timing for genetic testing. A few parents did find it too early to have genetic counseling in the first weeks following diagnosis, and a number of families pointed out that the flexibility offered to them by the counseling team was a contributing factor to them having a good experience with the early inclusion process. We also found that the time following diagnosis was experienced differently by families, some children only had days or weeks of symptoms before diagnosis where others had months and shifting diagnoses (from benign to malignant) before being given the final malignant diagnosis. Families belonging to this latter group tended to describe the diagnosis in more positive terms, as a confirmed diagnosis also provided these families with the opportunity to look forward and they saw the approach about WGS as part of that. At the same time, the intensity of a child's treatment as well as how affected the child was contributed to families' experiences of the weeks following diagnosis. Interviewed parents' views on the time of approach were independent of the child's diagnosis, prognosis, age, parental educational level, and parental gender, and families opposed to early introduction of WGS could thus not be identified before asking them. Based on the findings of this study families affected by childhood cancer can be offered WGS at the time of diagnosis, but flexibility from the approaching physician/clinical geneticist is paramount, as some families will want to push any decision about WGS.

### Meaningful informed consent

The discussion on meaningful informed consent is not novel in the field of pediatric oncology or genetics, and previous studies have found large gaps in parental knowledge of the research projects their child participated in (Kupst, Patenaude, Walco, & Sterling, 2003). When consent is given by a parent or a legal guardian on behalf of a minor to wide genomic mapping at a time of personal crisis the question of meaningful informed consent becomes omnipresent. Genetic information is complex and even when having understood the opportunity/risk of gaining information about primary findings, secondary findings and the implications for relatives, there is still an element of risk-taking which parents must accept going into WGS, as genetics professionals will never be able to give an exhaustive account of potential secondary findings. Ours and other studies have found that

parents feel overwhelmed by the circumstances around the time of diagnosis (Scollon et al., 2014, and Oberg et al., 2015), leading to the obvious question of whether parents are able to make an informed decision about WGS consent at a time of crisis. Some studies have suggested a two-step consent approach (Oberg et al., 2015), allowing for families to process information and to ask relevant questions arising between the first and second counselling sessions. Others have found that leniency and flexibility in regards to scheduling and offering more counseling sessions were the key to a meaningful informed consent (Scollon et al., 2014). We found that a number of parents did have concerns particularly in regards to potential secondary findings, and some parents expressed that they may well end up regretting their consent on that count. Other families had very in-depth discussions about how they imagined they would feel in case of a given scenario occurring. The authors interpret the interviewed parents' openness and debate about participation as a sign of them carefully having considered and agreed on participation with knowledge of the uncertainties involved. As did Scollon et al., we found that extending flexibility to families with regards to scheduling and to number of counseling sessions ensured that those families who had further questions and disagreements had the opportunity to ask and further discuss participation, which is essential if families are to have the time and space needed to make the right decision for them.

#### Discordant views between parents

This study did not include interviews with adolescents and the vast majority of families who participated had children between the ages 0-9. Only one out of the three interviewed families with an adolescent cancer patient insisted that their child had a decisive say in their decision to participate in WGS research. Indeed, in this case the child's wish to participate in the research was at odds with the mother's hesitation. The possibility of discordant preferences between adolescents and their parents when it comes to participating in pediatric cancer research has been explored in other studies (Ingersgaard, Tulstrup, Schmiegelow, & Baekgaard Larsen, 2017, and Levenseller et al., 2014) and it remains an area that requires further research in the context of pediatric WGS research, not least in light of debates around the right of the child to an open future (Johnson et al. 2017). Studies have also highlighted discordant views between professionals and parents when it comes to reporting of WGS findings (McCullough et al., 2016, and Levenseller et al., 2014). A significant finding emerging out of our study is that discordant preferences around reporting of WGS findings can and do exist between the parents of a child. While there is nothing surprising in the possibility of discordant preferences between two adults in itself, in the STAGING study parents need to agree to what findings they wish to have reported back. This can be complicated by situations of divorce where the parents of a child are not always communicating well with each other. Given the potential consequences of receiving information about disease predisposition, those parents who openly discussed their discordant preferences in counselling sessions or interviews suggested that as partners they were different kinds of people which could lead to different reactions to the findings that they receive from WGS of their child. In such cases, parents may need more time to deliberate which in turn suggests that more research on decision making processes in situations of parental discordance would be beneficial.

### High participation and full disclosure

A participation rate in the STAGING project of more than 80 percent suggests that parents see potential benefits as outweighing potential set-backs at the point of inclusion. This was confirmed in our interviews with parents who expressed concern about potential findings, yet in spite of this chose participation and for 14 out of 15 couples, also full disclosure of potential findings. This may reflect the situation most families are in when having a child diagnosed with cancer, in which there is no answer to the question of ‘why’ this has happened, and in which parents will do everything they can to improve every aspect of their child’s treatment and future health. Additionally, it is impossible to fully exclude undue influence on the part of the treating physician, clinical geneticist, anthropologist or research nurse, as the mere presentation of a project influences families. Anderson et al. looked at the effect of being presented with the option of WGS in patients referred to their genomic clinic for further assessment (Anderson et al., 2017). They found that being presented with the option of WGS induced an ‘inflicted ought’, meaning that while introducing the option of WGS can give freedom and possibilities, this may also present as a burden to some parents. STAGING can be viewed as an ‘inflicted ought’, hence the mere introduction of STAGING to parents is something they can never go back from and not have knowledge of. How parents will feel about their decision upon receiving WGS results is still not known, however, our findings show that interviewed parents opted for WGS with full knowledge of them potentially regretting their choice afterwards.

### Strengths and weaknesses

One of the weaknesses of our study is linked to its use of convenience sampling. Although we do have a diverse range of informants (in terms of educational background, age, income, diagnosis and time of approach), there were a number of families who agreed to an interview but where it proved difficult for them to find the time for it because of their life circumstances. It is likely that we have missed some issues related to families who are perhaps under more pressure whether because of their emotional state, social isolation or being disadvantaged. Finally, it should be mentioned that since this study is embedded in the STAGING project, there is an in-built tension in qualitatively examining how families experience being approached to participate in and how they reflect on WGS research (STAGING), while at the same time including patients in STAGING (clinical geneticist) and the PPS study (anthropologist). While interviews were used to allow parents a space outside of the genetic counselling session to give their views, we cannot disregard the possibility that some parents may have withheld some of their concerns.

A key strength of our study has been that it combined anthropological observations of genetic counselling sessions, systematic debriefings following these sessions as well as follow up interviews with parents. Our approach to parent perspectives is broader than an interest in their points of view on a given matter, rather in our study the overriding life circumstance of a pediatric cancer diagnosis has been our point of departure. From this perspective, a request to participate in WGS research is but one request among many to participate in a slew of research projects, and together these requests for participation are just one element in a life that is consumed by treatment of the cancer and care for the child. During the genetic counselling session and when asked concrete questions in follow up interviews, WGS is of course very present in the minds of parents. However,

research participation as a whole, plays a relatively small part in the lives of those families who are living with pediatric cancer. Our study has contributed insights into the actual process of deciding whether or not to participate in WGS research, i.e. how parents reason about being approached to participate in research at a time of crisis (timing); their decision to participate in WGS research (purpose); and their reservations (envisaged reactions). In this way the PPS builds on the multidisciplinary nature of the STAGING project which combines clinical genetics, anthropology, pediatric oncology, and bioinformatics.

## **Conclusion**

The majority of parents in this study found an early approach about WGS research acceptable. Still, since the weeks following diagnosis are experienced differently by parents, flexibility on the part of researchers is essential to ensure that all families are given the time and space they need to consider participation. WGS research in pediatric oncology is an emerging field and at this stage qualitative research (present study included) has only been carried out with families at the point of inclusion (McCullough et al., 2016) or with stakeholders who are asked to reflect on how they would hypothetically view WGS of pediatric patients (Levenseller et al. 2014, and Sapp et al., 2014). As a consequence, we only have insights into what parents anticipate from participation in WGS research. The jury is still out as to whether and how the reporting of findings will impact their lives. Nevertheless, what we found in our study was that some parents articulated ambivalence around their decision to opt for full disclosure, with some parents describing how they were genuinely torn between wanting full disclosure in order to prepare for the future and a concern that they might end up regretting that decision. Moreover, in some families there are discordant views between parents as to how much they would like to have reported back. We would therefore opt for a cautious interpretation of high participation rates in pediatric cancer WGS research and a tendency to opt for full disclosure. Follow up qualitative studies are required after reporting of findings, particularly in cases where disease predisposing findings are reported back to a family, but also in those cases where variants of uncertain significance are reported or indeed no findings are reported.

## **Author contribution:**

AW was responsible for the study and design. AB and AW conducted the analysis and prepared the initial manuscript draft. All authors contributed to the writing, rewriting and revision of the manuscript.

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Characteristics of patients and interviewed parents:

	N	%
<i>Patients</i>		
Gender		
Males	8	53
Females	7	47
Age		
0-4	8	53
5-9	4	27
10-14	2	13
15-18	1	7
Diagnosis		
Acute Lymphoblastic Leukemia (ALL)	3	20
Rhabdomyosarcoma	2	13
Wilms tumor	1	7
Mesoblastic nephroma	1	7
Ewing sarcoma	1	7
Osteogenic sarcoma	1	7
Burkitt Lymphoma	1	7
Langerhans cell histiocytosis	1	7
Blastic plasmacytoid dendritic cell neoplasm	1	7
Diffuse intrinsic pontine glioma (DIPG)	1	7
Atypical teratoid/rhabdoid tumor (ATRT)	1	7
Subependymal giant cell astrocytoma (SEGA)	1	7
<i>Parents</i>		
Gender		
Male	15	50
Female	15	50
Age		
≤ 30	1	3
31-35	5	17
36-40	13	43
41-45	8	27
≥ 46	3	10
Education (highest achieved degree)		
Primary/secondary school education	0	0
High school diploma	0	0
Vocational education	8	27
Short higher education (≤ 2years)	3	10
Bachelor degree (≤ 4 years)	12	40
Master's degree and/or PhD degree	7	23

### Inclusion characteristics

➤ Median days from diagnosis to short oral presentation and written material	8 (2-28*)
➤ Median days from diagnosis to genetic counselling	17.5 (7-42*)
➤ Median days from genetic counselling to interview	56.5 (27-105*)

\*90% range

### Box 1: Interview questions

- Could you describe the period leading up to the diagnosis of your child, how did you notice that something was wrong?
- How did you experience receiving the diagnosis?
- Can you recall when you were first approached about participating in research?
- What was your experience of being approached by researchers?
- Have you had any discussions at home about STAGING following your genetic counselling session, if so what kinds of questions or issues have come up?
- Which kind of findings have you decided to have reported back?

### Box 2: Debriefing questions

- Had the parents read the written information on STAGING that they had been provided with?
- Were the parents distressed during the counselling session in a way that might affect their understanding of the STAGING project?
- How is the contact and communication between genetic counsellor and parents during the counselling session?
- Have the parents agreed on which findings they would like to have reported back? If no, how are differing viewpoints expressed?
- Did the parents raise any concerns or worries regarding participation in STAGING during counselling? If yes, which kinds?
- Did those parents who would like to participate in STAGING articulate why they wanted to do so?

Figure 1: Pediatric cancer families inclusion in STAGING and PPS

