The psychological impact of genetic testing in childhood cancer: A systematic review.

Sophie Van Hoyweghen[1,2] · Kathleen Claes[1] · Robin de Putter[1] · Claire Wakefield[3,4] · Marieke Van Schoors[5] · Sabine Hellemans[1] · Lesley Verhofstadt[2]

[1]Department of biomolecular medicine, Faculty of medicine and health sciences, University of Ghent, Belgium;

[2]Department of experimental clinical and health psychology, Faculty of psychology and educational sciences, University of Ghent, Belgium

[3]School of Clinical Medicine, UNSW Medicine and Health, UNSW Sydney, Sydney, Australia;

[4]Behavioural Sciences Unit, Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia;

[5]Familieplatform VZW, Antwerp, Belgium;

sophie.vanhoyweghen@ugent.be

kathleen.claes@ugent.be

robin.deputter@ugent.be

c.wakefield@unsw.edu.au

marieke.vanschoors@familieplatform.be

sabine.hellemans@ugent.be

lesley.verhofstadt@ugent.be

Abstract

Objective: Cancer predisposition syndromes (CPSs) are being more frequently recognized in the etiology of pediatric oncology and genetic-related technologies are evolving rapidly, leading to an increasing availability of genetic testing for families. This systematic review assessed the psychological impact of genetic testing on children and parents in the context of childhood cancer. **Methods:** Searches were performed using three databases (Web of Science, Pubmed and Embase) to identify relevant empirical studies. Following Cochrane guidelines, we screened 3838 articles and identified 18 eligible studies, representing the perspectives of children and/or parents. **Results**: The included studies described the impact of genetic testing

in different contexts (e.g. predictive testing and diagnostic testing) and in different subgroups, (e.g. carriers and non-carriers). Overall, the studies did not identify clinically-relevant long-term increases in negative emotions (depression, anxiety, distress, uncertainty, guilt) as a result of genetic testing. Negative emotions were typically time-limited and generally occurred in families with particular characteristics (e.g. those with a history of multiple cancer diagnoses, families receiving an unfavorable result for one child and a favorable result in siblings, and those with pre-existing mental health difficulties). Positive emotions (hopefulness, relief and peace of mind) were also reported. Knowing their genetic risk status appeared to help to foster empowerment among families, regardless of the result and any associated emotions. **Conclusions**: Genetic testing in pediatric oncology does not appear to cause significant additional harm and can lead to positive outcomes. Clinicians need to be especially attentive when counseling families at increased risk of distress.

Keywords

Cancer, cancer predisposition, children, genetic testing, oncology, parents, pediatric oncology, psycho-oncology, psychological impact

Background

Advances in genetic technologies have led to the identification of more than 100 cancer predisposition genes and syndromes (CPSs).[1] Recent reports suggest that at least 10 % of children with cancer harbor a predisposing germline mutation or (likely) pathogenic variant/ (L)PV.[2,3] From a medical point of view, diagnosing a CPS in children with cancer is highly relevant for multiple reasons. First, the diagnosis can impact choice of therapy in patients; for instance, in some CPSs avoiding radiotherapy or deintensifying chemotherapy is recommended.[4,5] Mutation status can also be taken into account in the donor selection process

when related individuals act as stem cell donors.[6] Second, the child with cancer can benefit from adjusted surveillance for early detection of secondary malignancies. Due to the high-risk profile of these patients, this adjusted surveillance has a beneficial impact on mortality and morbidity[7], as well as on quality of life when prevention is possible.[8] Third, at-risk relatives can be offered predictive genetic testing[1] for the identified (L)PV and may also benefit from surveillance and/or preventive surgery.[9] Finally, transmission of a (L)PV to future offspring can be prevented with assisted reproductive techniques.[10] This may be relevant for the patients as they mature into adulthood as well as for the patients' parents if they are in their reproductive years and one or both is a carrier of a (L)PV. Given these potential health benefits, genetic testing for CPSs in pediatric oncology is of great medical interest to patients and their families.[11]

Despite this exciting medical potential, the short- and long-term psychological impact of genetic testing on children and their parents in the context of childhood cancer has yet to be systematically documented. Previous reviews have documented the impact of genetic testing in childhood across different health conditions, for example cardiovascular diseases[12], however no specific overview of the consequences of genetic testing for childhood cancer is available for clinicians. As every health condition has unique implications, a disease-specific overview is needed.

A comprehensive overview of the impacts of genetic testing in childhood cancer is clinically useful, as both clinicians and parents have raised ethical concerns about genetic testing for CPSs in children with cancer. When offering genetic testing to adults, four key principles are generally taken into account, including the patient's right to be fully informed, the right to autonomy in the decision-making process, the right to confidentiality, and the right not to know.[13] Fully respecting these principles becomes very complex when counseling minors

[1] The terms genetic testing and genetic screening are used interchangeably throughout the text.

as their cognitive and emotional development is still ongoing, which limits their capacity to be fully informed and engaged in an autonomous decision-making process. When a patient is too young, parents are generally appointed as representatives since they are presumed to act in a child's best interest[14], but this compromises the child's right to confidentiality and their right not to know.[15,16] Parents often then decide to what extent their child's results are communicated with them, however this can be challenging, if parents are neither fully aware nor informed about the possible psychological impact of genetic testing on themselves and their child(ren).

Although the impact of genetic testing on children is theoretically assumed in ethical papers[17-19], it is often unclear for clinicians which of these considerations and assumptions are grounded in empirical evidence. For example, Ackerman (1996) posited multiple possible adverse psychological reactions that children might experience after genetic testing, such as increased anxiety about future health, guilt about being "bad", or decreased self-esteem. Despite the intuitive appeal of these assumptions, at that time there was little empirical research to support these assertions. The potential disadvantage of these assumptions is that in the absence of an overview of the existing empirical research, clinicians may feel hesitant to offer genetic testing in the context of childhood cancer.

Therefore, the first aim of this systematic review was to critically assess the available empirical evidence regarding the psychological impact of genetic testing in childhood cancer for both children and their parents, in a diagnostic as well as a predictive setting. Our findings will be directly relevant for clinicians working with patients and their families by providing them with a summary of knowledge that can empirically guide counselling practices with this population. The secondary aim was to examine theoretical, methodological and statistical issues in the existing literature and formulate recommendations for future research.

Materials and methods

We followed the Cochrane guidelines[20] to ensure comprehensiveness and reliability, while minimizing the chance of bias[21]. We undertook the following steps: (a) formulation of the scope of the review and research questions; (b) thorough literature search; (c) detailed data extraction; and (d) integration of the major findings and implications. As quantitative data on the psychological impact of genetic testing in childhood cancer is limited, we also included qualitative studies. Given this, we did not conduct a meta-analysis. The study protocol is available upon request.

Literature search

Web of Science, PubMed, and Embase were searched using the following search terms: [Child* OR p$ediatric* OR adolescen* OR youth OR AYA OR infan* OR minor* OR teen* OR parent* OR young person* OR young people OR mother* OR father*] AND [exome sequencing OR genetic service* OR genetic testing OR genetic screening OR genetic counsel$ing OR genomic testing OR genomic sequencing OR next generation sequencing OR genome sequencing OR diagnostic testing OR multigene cancer panel testing OR parallel sequencing] AND [cancer* OR tumo$r OR oncolog* OR malignanc* OR hereditary OR family cancer syndromes OR cancer predisposition OR cancer susceptibility OR predisposition syndrome] AND [psycholog* OR psychosocial OR impact OR adaptation OR adjustment OR emotion* OR experience* OR perspective*]. These search terms were selected in collaboration with a library information specialist from the Knowledge Centre of Healthcare Ghent (KCGG; Ghent University Hospital, Belgium) and three researchers familiar with the field. Search results were exported to Endnote X9; reference lists of the eligible studies were reviewed to ensure inclusion of all relevant papers.

Inclusion and exclusion criteria

Articles were selected for inclusion if they: a) assessed the psychological impact of genetic testing in childhood cancer, and b) included a pediatric sample (children younger than 18 years old) in which the impact on parents and/or children was examined. Studies published in languages other than English and non-empirical articles (i.e. theoretical work, reviews, case reports, books, book chapters, reviews, commentaries, practice guidelines, conference abstracts, and dissertations) were excluded. No studies were excluded based on the year of publication.

Data extraction

In January 2022, we identified 5651 articles and exported them to EndnoteX9. After deduplicating, two authors (S.V.H. and S.H.) independently screened all the remaining 3838 articles by title and abstract (with an inter-rater agreement of 94%). Any disagreements were resolved through discussion. If an abstract fulfilled all inclusion criteria, we extracted the full-text article (100% screened by S.V.H. and 50% by S.H.; 83% inter-rater agreement). Of the 53 reviewed full-texts, 16 met our inclusion criteria. After screening the study reference lists, no additional studies needed to be included. The main findings and characteristics from each study were extracted and listed in Supplementary Table 1. Afterwards, a narrative synthesis was conducted by S.V.H. An updated search was done in March 2023, identifying two additional eligible articles, leading to 18 included studies. The findings from these two studies were incorporated into the narrative synthesis. Figure 1 summarizes the data extraction procedure in a PRISMA flow diagram.

The scientific quality of all included studies was assessed by the first author (S.V.H) using the criteria published in Alderfer et al. (2010). Nine aspects were evaluated in the quantitative studies, including explicit scientific purpose, appropriateness of design and analysis, measurement reliability, statistical power, internal validity, measurement validity,

external validity, appropriate discussion, and knowledge contribution. Eleven aspects were evaluated in the qualitative studies, including explicit scientific purpose, appropriateness of design and analysis, grounding results in examples, integration of finding into a framework, specification of author's perspective, accurate and understandable topic area, appropriateness of the sample, credibility checks, description of sample, appropriate discussion and contribution to knowledge.[22] Each aspect was rated on a 3-point scale ranging from 1 = "no or little evidence in fulfilling the criterion or low quality" to 3 = "good evidence or high quality". Afterwards, an overall score for scientific merit for each study was calculated by averaging all aspect scores. To assure the reliability of the quality assessment, S.H. double coded 50% of the included studies, with single measure and average measures intraclass correlation coefficients of .86 and .92, respectively, demonstrating good interrater reliability. Supplementary Table 2 gives an overview of the scores given by both authors. Based on these quality ratings no studies were excluded.

Results

PART 1 Characteristics of reviewed studies

The methods and findings are summarized in Supplementary Table 1. Of the 18 included studies, 10 were qualitative (56%), 4 were quantitative studies (22%) and 4 used a mixed methods design (22%). Twelve studies were cross-sectional (67%), the others were longitudinal (n = 6, 33%). Sample sizes varied from 7 to 114 participants. In six studies only children participated (33.3%), whereas in six other studies only parents participated (33.3%). The remaining six studies included both children's and parents' perspectives (33.3%), with one study surveying only mothers and children.

Genetic testing for different oncology conditions (and the related genes) were included in the studies. Six studies examined the impact of broad testing for Cancer Predisposition Syndromes (33.3%) and six studies specifically focused on testing for Familial Adenomatous Polyposis (*APC* gene; 33.3%). Other studies examined the impact of testing for Li-Fraumeni Syndrome (*TP53* gene; n = 2, 11%), Familial Atypical Multiple Mole Melanoma Syndrome (*CDKN2A* gene; n = 2, 11%), Multiple Endocrine Neoplasia type 2 (*RET* gene; n = 1, 5.6%), and Familial Retinoblastoma (*RB1* gene; n = 1, 5.6%). Eight studies examined the impact of predictive testing (44.4%), six studies examined the impact of diagnostic testing (33.3%) and in four studies no distinction between the context for testing was made (22.2%).

PART 2 Quality of reviewed studies

On average, the scientific merit ratings[22] of the studies was good and ranged from 2.2 to 3 on the 3-point scale used, with an overall mean of 2.54 (Supplementary Table 2).

Theoretical considerations. None of the included studies reported using a theoretical framework to guide the research questions, selected variables or interpretation of the results. This potentially led to a more arbitrary approach and could limit progression of the research field as theories stay untested and unrevised. Furthermore, in qualitative articles, the perspectives or theoretical orientation of the authors was not often made explicit.

Methodological considerations. Two quantitative studies[23,24] and two mixed-method studies[25,26] mentioned that they had limited power due to a small sample size, and recommended that any conclusions must be treated with caution. Also, half of the quantitative and mixed method studies (N = 4)[25,27-29], gathered data at a single time point, precluding longer term assessment of the impact of genetic testing, limiting the identification of contributing factors and preventing any causality conclusions. In addition, some studies did not mention their participant response rate[23,27,29,30] and any differences between participants and non-participants were often not

reported[24,26,31-38], limiting external validity. Furthermore, only one study used a validated questionnaire to measure the impact of genetic testing[28]. Rather, in each quantitative study, the authors either choose a non-validated specific questionnaire[29,39] or one or more validated, but non-specific questionnaires[23-27,29] that they perceived to best fit the particular topic or variables they intended to measure.

PART 3 Narrative summary of reviewed studies

The narrative review is divided in two sections based on (1) the perspectives of parents and (2) the perspectives of children. Each section is then organized by three domains of psychological impact that emerged from the literature: (a) negative emotions (including psychological distress, worry, loneliness, guilt, disappointment, and uncertainty), (b) positive emotions (including comfort, reassurance, joy, relief, and hope) and (c) empowerment (including a sense of control, feeling prepared, and increased power). For each theme, the number and types of relevant studies are reported, followed by the findings generalized across the different oncology conditions.

Parents' emotions

Negative emotions. This theme was addressed in six qualitative[30,32,34,35,37,40], three quantitative[23,24,39] and three mixed method[26-28] studies.

Overall, reports of *psychological distress* following genetic testing were low, both for parents receiving unfavorable (i.e. (L)PV was found) and favorable (i.e. no (L)PV was found) results. Indeed, most parents did not perceive genetic testing as particularly burdensome.[23,24,26,28,30,32,34,35,37,39,40] For example, in two studies, no clinically significant levels of depression, anxiety and distress were found during follow-up.[23,24] Only one study reported that parents showed moderate to high levels of anxiety after receiving an unfavorable test result

for their child, with disturbed daily activities in 43% of these parents.[27] However, parents' depressive feelings stayed within normal limits in this study.[27]

Some parents did however experience negative emotions after genetic testing. More specifically, in three studies parents indicated that they experienced *worry* about their children's health. The content of this worry varied depending on the nature of the testing. In case of predictive testing, some parents were concerned about unnoticed disease progress, while in the case of diagnostic testing some parents expressed concerns about secondary cancer development.[27,30,39] Moreover, worries about their children's risk for malignancies were higher in carrier parents (who had the mutation themselves) than in noncarriers and no-test control parents. In contrast, no-test control parents reported greater worry than noncarrier parents[39], showing that the presence of these concerns is not always linked to a test result in the child.

Parents also experienced feelings of *loneliness*, *guilt* and *disappointment*. Some parents reported feeling lonely when their child received an unfavorable test result, particularly if their child's condition was rare.[28] Some parents also felt responsible for the development of the cancer in their child when the (L)PV is passed on by (one of) the parents.[30] Parents appeared to be affected by more feelings of guilt when more generations were affected in the family, as they felt they should have identified the increased cancer risk in their family sooner. Although parents rationally realized that the possibility of passing on a (L)PV is not their fault, parents who received a favorable test result shared that it helped allay some of their guilt and feelings of blame.[30,34,35] However, it was also possible for parents to feel disappointed when their child received a favorable test result after diagnostic testing as they had hoped to find an explanation for the cancer development in their child.[32,34] Thus, for some parents receiving a favorable test result did not appear to make coping with their child's cancer harder, but it also did not always bring solace.[28]

It is important to note that the experience of negative emotions after genetic testing varied considerably across parents and seemed to be especially associated with specific *individual or contextual characteristics.*[23,27,32,39] Parents who received different results across their children (i.e. favorable and unfavorable results across siblings), experienced more anxiety and depression than parents who received the same result for all their children.[23,27] It appeared that it was not the genetic testing that impacted their distress, but the difference in outcome for their children that made it difficult for parents to cope. Further, in one study, parents with a lower level of education reported more distress than those with a higher level of education.[27] Another study reported that parents with a more pessimistic view of the future or high pre-existing levels of distress experienced genetic testing as more burdensome.[27,32] Gender may also be important: women reported in general more negative emotions than men in one study.[39]

Positive emotions. This theme was addressed in six qualitative[30,32,34,35,37,40], one quantitative[39] and three mixed-method[26-28] studies.

Many parents also reported positive experiences after genetic testing. If their child received a favorable test result after predictive and diagnostic testing, parents expressed feelings of *comfort, reassurance* and even *joy.*[28,35] Moreover, receiving a favorable predictive test result improved the quality of their lives, as felt they no longer had to worry about the onset of cancer in their children.[27]

Finally, many parents felt *relieved,* due to the removal of uncertainty, both in case of receiving a favorable or unfavorable result for their child.[26-28,32,34,37] When receiving a favorable result, parents described the relief as increasing their sense of peace of mind. When receiving an unfavorable result, some parents shared that they felt relief of the uncertainty and a sense of satisfaction of their curiosity.[27,34] Indeed, some parents reported that coping with uncertainty was more burdensome than coping with an unfavorable result.[30,40]

Empowerment. This theme was addressed in four qualitative studies[30,32,37,40] and one quantitative study.[39]

The (possibility of a future) cancer diagnosis in a child makes life unpredictable. Parents stressed that opting for genetic testing gave them a little more *sense of control*. Regardless of the outcome or the emotions associated with it, some parents expressed that they felt empowered by the knowledge of their child's genetic status and therefore more certain about the future.[30,37,40] Even in case of receiving an unfavorable result, parents reported that they felt empowered and more prepared to manage the risk, as they could now focus on the advantages of having this knowledge, such as adjusted surveillance.[32,39]

Children's emotions

Negative emotions. This theme was addressed in six qualitative[31,33,36-38,40], four quantitative[23,24,29,39] and three mix method studies.[25,26,28]

In general - regardless of the outcome of the genetic testing - clinically increased *psychological distress* after genetic testing in children was rare.[23,24,26,28,29,31,33,36-40] Most studies focused on anxiety, depression and/or worry. When these emotions were reported, adolescents[2] generally described them as 'mild'. Over time, levels of *anxiety, depression* and *worry* remained low, or were transient.[23,26,38] Parents also observed no changes in the mental or physical health in their child after testing.[40] Furthermore, adolescents appeared to understand the implications of the genetic testing and the possible high-risk status associated with an unfavorable result. While some adolescents reported that they needed time to let their results 'sink in', they typically accepted the result without experiencing significant levels of negative emotions.[26,31] Only in the study of Michie et al. (2000) there was a trend for children receiving unfavorable

[2] When the term adolescents is used explicitly instead of children, the results only refer to those aged 10 years or older (Sawyer et al., 2018)

results to be more anxious and depressed than those receiving favorable results. However, the children's mean scores for anxiety and depression were within the normal range.

It is important to note that some studies did describe two specific negative emotions when children received an unfavorable genetic test result. First, some children experienced feelings of *loneliness*. They reported feeling alienated from others because being diagnosed with a CPS is very rare.[28,38] Second, some children indicated that they *felt uncertain* at times because of the genetic testing. More specifically, although genetic testing reduced the uncertainty about their mutation status, it created a new uncertainty about living with an increased (multi-organ) cancer risk with an uncertain penetrance for tumor development in their future.[36,38]

Finally, several studies found that negative emotions in children after genetic testing seemed to be more prevalent in specific families with particular *individual or contextual characteristics*. More specifically, children reported that witnessing distress in their parents was more stressful than inheriting a mutation itself.[33] Moreover, children with a (L)PV-positive mother with cancer, had significantly higher depression and anxiety scores after testing, regardless of their own test results.[23,25] In contrast, children with affected fathers showed a decrease in negative emotions after testing.[23,24] Children can also be influenced by their siblings' results. For example, children reported feeling more anxious and guilty when a CPS was found in their sibling instead of in themselves.[24,31] The age of testing also appeared to be important, with late adolescence being a particularly vulnerable period.[25] Indeed, adolescents wanted to learn about their CPS at an age they were old enough to understand it, but young enough to incorporate it into their life.[38]

Positive emotions. This theme was addressed in five qualitative studies[31,33,37,38,40], two quantitative studies[29,39] and one mix method study.[28]

Children who underwent genetic testing, reported positive emotions as well next to the negative emotions described above. In general, children experienced a sense of *relief* and *hope* when receiving their genetic test results. In the event of a favorable result, receiving good news was experienced as a form of closure as they learnt that they were not more at risk than other children.[37,39] Interestingly, children also mentioned feeling relieved as a consequence of witnessing relief in their parents.[33]

In the event of an unfavorable result, some children reported feeling *relieved* of uncertainty and hopeful about having better health outcomes than older generations in their family, now that they were aware of their predisposition.[28,33] Regardless of their result, adolescents typically stated that the benefits of genetic testing outweighed the drawbacks, providing additional clarity about what is important and of value in life.[31,33]

Empowerment. This theme was addressed in five qualitative studies[31,33,36-38], one quantitative[39] and one mixed-method study.[26]

Adolescents often described experiencing some sort of empowerment when undergoing genetic testing, regardless of the result and the emotions they experienced. Knowing their genetic risk status helped them to feel prepared to manage the risk and gave them more agency to make informed life decisions.[31,36,39] They shared that they felt more able to plan for the future[33] and were less worried, even when receiving an unfavorable result, as they knew steps could be taken to protect themselves.[26] In addition, in terms of self-concept, some adolescents indicated that although their tumor risk had influenced their self-concept, they did not feel defined by it. They shared that it had not changed their sense of who they were or what they wanted to do with their lives.[31,38] In case of a favorable test result, the study of Michie et al. (2001) showed even an increase in self-esteem of non-carrier children.

Discussion

This review of 18 studies aimed to provide clinicians with a summary of current literature on the impact of genetic testing for childhood cancer predispositions and assist them in guiding families.

Across the included studies, clinical levels of commonly reported psychological domains - such as anxiety, depression and distress - among parents and children after genetic testing were rarely reported. These findings are in line with a systematic review focusing on the impact of childhood genetic testing in different health conditions[12] and with the onco-genetic testing literature in adults.[41] There are a couple of possible explanations for this low prevalence of clinically relevant distress. It is possible that genetics professionals now provide evidence-based counseling in a rigorous and attentive way, being mindful of any anticipated psychological vulnerability of families. Interestingly, earlier studies at the commencement of genetic testing in childhood cancer, in the late 1990s and early 2000s, reported more distress[23,27], than more recent publications.[31,32,39] One could also hypothesize that there may be a bias in genetic testing participation towards more resilient families. It could be that families who anticipate feeling too overwhelmed by a possible unfavorable genetic test result will not opt for genetic testing. Adult onco-genetics literature also shows that fear of an unfavorable result can be an important reason for people not to initiate genetic testing.[42] Or, it may be that if families do consent for genetic testing, more distressed families feel too overwhelmed to participate in research about their experiences. Additionally, it has been reported that the measures used to evaluate impact of genetic testing are not always appropriate as they lack sensitivity and specificity to capture the unique concerns that surround genetic testing.[43]

In contrast with the absence of clinically elevated levels of distress, some specific negative emotions were reported across studies, including loneliness, uncertainty, worry, and

guilt. Receiving a cancer diagnosis in childhood is rare. The diagnosis of a CPS, however, is even rarer, which can make families feel even more "alone". This rarity can make it hard to share experiences, relate or talk about it with others, especially when the mutation is a de novo (L)PV and the child is the first person affected in the family. In other studies examining the impact of rare diseases, families frequently report experiencing this kind of social isolation.[44,45] In addition, feelings of uncertainty seem inherent to coping with an increased risk of tumor development. Any new certainty regarding the increased risk of cancer, can then lead to new uncertainties as it is not known if and when a new tumor will develop. Consistent with studies on other hereditary conditions, transmission guilt in parents and survivor's guilt in non-carrier children and/or parents was also reported.[46] However, in general, included families did not describe these emotions as overwhelming.

Negative emotions after genetic testing often coexist with a range of positive emotions and a sense of empowerment. The included studies found evidence for feelings of relief, hopefulness for better health outcomes and a sense of control in parents' and children's lives. Similar positive experiences and psychological benefits are found in studies on adult genetic testing.[47,48] A possible explanation for these positive findings could be that not knowing is experienced as more distressing than clarifying their risk status. In the event of a favorable test result, children can proceed with their lives as though there is no increased risk of developing cancer. In the event of an unfavorable result, the future becomes somewhat clearer. Parents and children can also experience increased agency, as more informed life decisions can be made. Parents and children valued the steps that could be taken in terms of adjusted surveillance programs to protect themselves or their families and some expressed an increased appreciation of life with new perspectives and values.

Several interesting parallels can be drawn from the included studies. First, parallels can be found between favorable and non-favorable genetic testing results. In both cases, all three

categories, i.e. positive emotions, negative emotions and empowerment, were experienced. A favorable result is not exclusively related to positive emotions and an unfavorable result is not exclusively related to negative emotions. In fact, genetic testing appears to impact a complex range of different emotions. Second, the impact of predictive testing and diagnostic testing can be experienced quite similarly. This is surprising since these families initiate testing from a different position, i.e. with a healthy child or with a child with cancer. However, no strong conclusions can be drawn due to the small sample sizes of the included studies. Third, a parallel can also be found in the experiences of parents and children. Both groups experienced negative emotions, positive emotions and feelings of empowerment, and even within these three categories, similar aspects tended to be reported.

Finally, some individual and contextual characteristics appear to moderate the impact of genetic testing. Consistent with findings from previous studies of hereditary cancer and cardiovascular syndromes[46,49-51], people with pre-existing mental health issues, people with a lower education level and women in general reported higher levels of distress. Further, the child's age at testing appears to influence the experienced impact, where late adolescence is a more vulnerable period to learn about their genetic status than early adolescence or childhood. This finding should be treated with caution, since there appears to be no consensus in literature regarding the optimal period for genetic testing. However, in a qualitative study on the experiences of adolescents in genetic counseling for different health conditions, late adolesence was described as a better period for testing than early adolescence.[52] At this age, there is a greater maturity and willingness to comprehend the information provided in the genetic counseling. On the other hand, in the systematic review of Wakefield et al. (2016) applying the 'earliest onset' rule to protect the child's autonomy was suggested. In that case, genetic testing is recommended to only be offered to children at the earliest age of condition onset. However, if this would be during adolescence, testing at a younger age can be considered.

At the contextual level, two characteristics seem to play an important moderating role. First, families experienced more distress when receiving different genetic test results across children (i.e. favorable and unfavorable). We could hypothesize that these children and their parents may experience more distress due to conflicting feelings as a consequence of the different results. It might be difficult for parents to explain to their children why they will be treated differently and to cope - as a family - with the fact that they have not all been given equal life chances.[27] In these families, siblings with a favorable test result often report experiencing survivor's guilt[24,31], as is also described in a systematic review focusing on the impact of childhood genetic testing in different health conditions.[12] In addition, differential test results can also affect family dynamics. For example, by increasing levels of conflict or by challenging their sense of cohesion and belonging as a family as a whole. Second, children experience their own genetic testing as more difficult when witnessing distress or illness in a parent. It is possible that they interpret the severity of a test result (partly) based on their parents' reaction. This is in line with the social learning theory[53] and the interpersonal role of pain, where high levels of parental catastrophizing and distress are associated with increased levels of child distress.[54] It could also be that children have developed a mental picture of their future by identifying with their parents' illness trajectory. Indeed, a previous study showed that the experience of parental cancer in childhood is a risk factor for psychological distress because children feel more at risk of becoming ill themselves, regardless of the disclosed genetic result.[55]

Suggestions for future research

It would be useful to develop and validate more specific questionnaires examining the impact of genetic testing in childhood cancer. In addition, more longitudinal studies -with time points prior, during and after genetic testing - are needed to gain a deeper understanding of the impact and to uncover causal relationships. Moreover, due to the rarity of CPS and to better understand if and how experiences may differ in CPS-families it would be valuable to have

larger sample sizes, necessitating international collaboration. Also, as large panel testing is used more frequently in genetic testing, more variants of uncertain significance will be discovered and communicated. This too will require additional attention in future research as this experience will differ from an (un)favorable result.

Finally, based on the results of this review, we can conclude that individual impacts of genetic testing appear to be influenced by contextual characteristics. Indeed, genetic testing not only affects the patient's being, but also his or her family. Therefore, it is essential in future research to examine more closely the impact experienced by all family members –including siblings - and the family as a whole (such as the degree of cohesion, conflict and expressiveness). This will require family level responses involving multiple members within families.

Clinical implications

Several clinical recommendations for genetic counseling in pediatric oncology arise from the results of this review. First, there is a need to properly address any present negative emotions, but there is also an opportunity to explore the positive emotions and feelings of empowerment following a favorable and unfavorable result. Second, although most parents and children adapt well, clinicians should be sensitive to individual and contextual characteristics of families undergoing genetic testing that may increase their risk of distress, for example pre-existing mental difficulties or differential results between siblings. Third, since a genetic testing result affects the entire family, genetic counseling should be directed toward both parents and children, with particular consideration of the family as a whole. Therefore, careful, developmentally sensitive and time sensitive pre- and post-counseling, tailored to the needs of the child and its family is essential to guide them first in their informed decision-making and later in the processing of the result. Dedicating sufficient time to this will improve the patients'

experience and understanding. Finally, also broadening the systemic view to a multi-family contact and peer-to-peer support can be helpful and beneficial for patients. It may for example decrease feelings of loneliness and can stimulate new perspectives or improve learning new coping strategies.

Study limitations

This review described the impact of genetic testing in the context of childhood cancer, and included all studies examining this. However, different studies assessed the impact of different CPSs, leading to a highly heterogeneous sample. Depending on which CPS is diagnosed, the consequences can be very different and thus have a different impact. In addition, CPSs in children are rare, which also results in a scarcity of studies investigating the impact of genetic testing on children and parents. Moreover, these studies often do not include very large samples, which required us to generalize across the different oncology conditions and thus no findings are specifically linked to the different mutations. Based on the included papers, there appears to be little difference in impact related to the specific CPSs. Moreover, other factors appear to be more determinative of impact, such as contextual aspects. However, this does not exclude the possibility that there is nevertheless a different impact between CPSs. It appears for now that several findings from the included studies apply to both diagnostic testing and predictive testing and in both parents and children, across different CPSs. However, due to the limitations indicated, we should be cautious in drawing conclusions and further research is needed to strengthen these findings and to examine differences and similarities more closely between these groups.

Conclusions

Overall, there seemed to be limited detrimental impact on the psychological wellbeing of children and parents undergoing genetic testing in childhood cancer. Yet, some

characteristics in families may moderate the impact and lead to poorer psychological outcomes. At the same time, there appears to be also evidence for positive emotions and feelings of empowerment as a result of genetic testing. Awareness of these emotions and cognitions after genetic testing and the potential moderators is important for clinicians providing genetic counseling and will help them in guiding and supporting families.

References

1. Scollon S, Anglin AK, Thomas M, Turner JT, Wolfe Schneider K. A Comprehensive Review of Pediatric Tumors and Associated Cancer Predisposition Syndromes. *Journal of genetic counseling.* 2017;26(3):387-434.
2. Gröbner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. *Nature.* 2018;555(7696):321-327.
3. Desrosiers LR, Quinn E, Cramer S, Dobek W. Integrating genetic counseling and testing in the pediatric oncology setting: Parental attitudes and influencing factors. *Pediatric blood & cancer.* 2019;66(10):e27907.
4. Suri JS, Rednam S, Teh BS, Butler E, Paulino AC. Subsequent Malignancies in Patients With Li-Fraumeni Syndrome Treated With Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2013;87(2):S71-S72.
5. Sirák I, Šinkorová Z, Šenkeříková M, et al. Hypersensitivity to chemoradiation in FANCA carrier with cervical carcinoma-A case report and review of the literature. *Rep Pract Oncol Radiother.* 2015;20(4):309-315.
6. Kallen ME, Dulau-Florea A, Wang W, Calvo KR. Acquired and germline predisposition to bone marrow failure: Diagnostic features and clinical implications. *Semin Hematol.* 2019;56(1):69-82.
7. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol.* 2016;17(9):1295-1305.
8. Lammens CR, Bleiker EM, Aaronson NK, et al. Regular surveillance for Li-Fraumeni Syndrome: advice, adherence and perceived benefits. *Fam Cancer.* 2010;9(4):647-654.
9. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol.* 2010;28(5):893-901.
10. Offit K, Kohut K, Clagett B, et al. Cancer genetic testing and assisted reproduction. *J Clin Oncol.* 2006;24(29):4775-4782.
11. Brozou T, Taeubner J, Velleuer E, et al. Genetic predisposition in children with cancer - affected families' acceptance of Trio-WES. *Eur J Pediatr.* 2018;177(1):53-60.
12. Wakefield CE, Hanlon LV, Tucker KM, et al. The psychological impact of genetic information on children: a systematic review. *Genet Med.* 2016;18(8):755-762.
13. Yang M, Kim JW. Principles of Genetic Counseling in the Era of Next-Generation Sequencing. *Ann Lab Med.* 2018;38(4):291-295.
14. Salter EK, Hester DM, Vinarcsik L, et al. Pediatric Decision Making: Consensus Recommendations. *Pediatrics.* 2023;152(3).
15. Botkin JR, Belmont JW, Berg JS, et al. Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am J Hum Genet.* 2015;97(1):6-21.

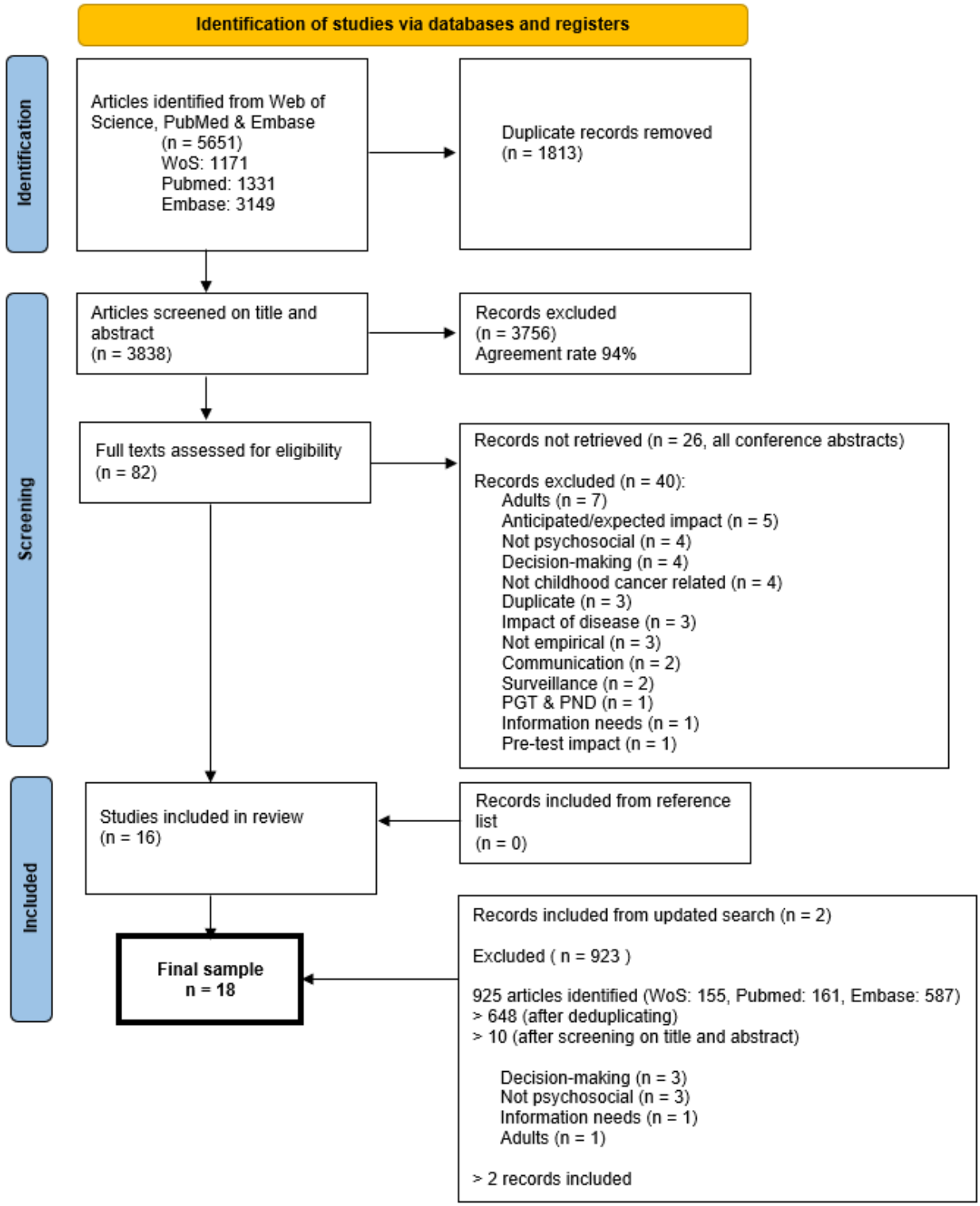
16. MacDonald DJ, Lessick M. Hereditary cancers in children and ethical and psychosocial implications. *J Pediatr Nurs.* 2000;15(4):217-225.
17. Ackerman TF. Genetic testing of children for cancer susceptibility. *J Pediatr Oncol Nurs.* 1996;13(1):46-49.
18. Grosfeld FJ, Lips CJ, Beemer FA, van Spijker HG, Brouwers-Smalbraak GJ, ten Kroode HF. Psychological risks of genetically testing children for a hereditary cancer syndrome. *Patient education and counseling.* 1997;32(1-2):63-67.
19. Tischkowitz M, Rosser E. Inherited cancer in children: practical/ethical problems and challenges. *Eur J Cancer.* 2004;40(16):2459-2470.
20. Higgins JPT, Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., & Welch, V.A. . Cochrane Handbook for Systematic Reviews of Interventions version 6.3 2022; http://www.training.cochrane.org/handbook.
21. Eiser C, Hill JJ, Vance YH. Examining the psychological consequences of surviving childhood cancer: systematic review as a research method in pediatric psychology. *J Pediatr Psychol.* 2000;25(6):449-460.
22. Alderfer MA, Long KA, Lown EA, et al. Psychosocial adjustment of siblings of children with cancer: a systematic review. *Psycho-Oncology.* 2010;19(8):789-805.
23. Codori AM, Petersen GM, Boyd PA, Brandt J, Giardiello FM. Genetic testing for cancer in children. Short-term psychological effect. *Arch Pediatr Adolesc Med.* 1996;150(11):1131-1138.
24. Codori AM, Zawacki KL, Petersen GM, et al. Genetic testing for hereditary colorectal cancer in children: long-term psychological effects. *Am J Med Genet A.* 2003;116a(2):117-128.
25. Gjone H, Diseth TH, Fausa O, Nøvik TS, Heiberg A. Familial adenomatous polyposis: mental health, psychosocial functioning and reactions to genetic risk in adolescents. *Clin Genet.* 2011;79(1):35-43.
26. Stump TK, Aspinwall LG, Kohlmann W, et al. Genetic Test Reporting and Counseling for Melanoma Risk in Minors May Improve Sun Protection Without Inducing Distress. *Journal of genetic counseling.* 2018;27(4):955-967.
27. Grosfeld FJ, Beemer FA, Lips CJ, Hendriks KS, ten Kroode HF. Parents' responses to disclosure of genetic test results of their children. *Am J Med Genet.* 2000;94(4):316-323.
28. McGill BC, Wakefield CE, Vetsch J, et al. "I remember how I felt, but I don't remember the gene": Families' experiences of cancer-related genetic testing in childhood. *Pediatric blood & cancer.* 2019;66(8):e27762.
29. Michie S, Bobrow M, Marteau TM. Predictive genetic testing in children and adults: a study of emotional impact. *Journal of medical genetics.* 2001;38(8):519-526.
30. Hill JA, Gedleh A, Lee S, Hougham KA, Dimaras H. Knowledge, experiences and attitudes concerning genetics among retinoblastoma survivors and parents. *Eur J Hum Genet.* 2018;26(4):505-517.
31. Alderfer MA, Lindell RB, Viadro CI, et al. Should Genetic Testing be Offered for Children? The Perspectives of Adolescents and Emerging Adults in Families with Li-Fraumeni Syndrome. *Journal of genetic counseling.* 2017;26(5):1106-1115.
32. Bon SBB, Wouters RHP, Hol JA, Jongmans MCJ, van den Heuvel-Eibrink MM, Grootenhuis MA. Parents' experiences with large-scale sequencing for genetic predisposition in pediatric renal cancer: A qualitative study. *Psycho-Oncology.* 2022;31(10):1692-1699.
33. Duncan RE, Gillam L, Savulescu J, Williamson R, Rogers JG, Delatycki MB. "You're one of us now": young people describe their experiences of predictive genetic testing for Huntington disease (HD) and familial adenomatous polyposis (FAP). *Am J Med Genet C Semin Med Genet.* 2008;148c(1):47-55.
34. Malek J, Slashinski MJ, Robinson JO, et al. Parental Perspectives on Whole Exome Sequencing in Pediatric Cancer: A Typology of Perceived Utility. *JCO precision oncology.* 2017;1.
35. Malek J, Pereira S, Robinson JO, et al. Responsibility, culpability, and parental views on genomic testing for seriously ill children. *Genet Med.* 2019;21(12):2791-2797.

36. Forbes Shepherd R, Werner-Lin A, Keogh LA, Delatycki MB, Forrest LE. "I need to know if I'm going to die young": Adolescent and young adult experiences of genetic testing for Li-Fraumeni syndrome. *Journal of psychosocial oncology.* 2021;39(1):54-73.
37. Waldman L, Hancock K, Gallinger B, et al. Perspectives and Experiences of Parents and Adolescents Who Participate in a Pediatric Precision Oncology Program: "when You Feel Helpless, This Kind of Thing Is Very Helpful". *JCO Precision Oncology.* 2022;6.
38. Weber E, Shuman C, Wasserman JD, et al. "A change in perspective": Exploring the experiences of adolescents with hereditary tumor predisposition. *Pediatric blood & cancer.* 2019;66(1):e27445.
39. Aspinwall LG, Stump TK, Taber JM, et al. Genetic test reporting of CDKN2A provides informational and motivational benefits for managing melanoma risk. *Transl Behav Med.* 2018;8(1):29-43.
40. Kattentidt-Mouravieva AA, den Heijer M, van Kessel I, Wagner A. How harmful is genetic testing for familial adenomatous polyposis (FAP) in young children; the parents' experience. *Fam Cancer.* 2014;13(3):391-399.
41. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol.* 2009;28(4):510-518.
42. Willis AM, Smith SK, Meiser B, Ballinger ML, Thomas DM, Young MA. Sociodemographic, psychosocial and clinical factors associated with uptake of genetic counselling for hereditary cancer: a systematic review. *Clin Genet.* 2017;92(2):121-133.
43. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol.* 2002;21(6):564-572.
44. Nevin SM, McLoone J, Wakefield CE, Kennedy SE, McCarthy HJ. Genetic Testing in the Pediatric Nephrology Clinic: Understanding Families' Experiences. *J Pediatr Genet.* 2022;11(2):117-125.
45. Nevin SM, Wakefield CE, Barlow-Stewart K, et al. Psychosocial impact of genetic testing on parents of children with developmental and epileptic encephalopathy. *Developmental Medicine and Child Neurology.* 2022;64(1):95-104.
46. Bordet C, Brice S, Maupain C, et al. Psychosocial Impact of Predictive Genetic Testing in Hereditary Heart Diseases: The PREDICT Study. *Journal of clinical medicine.* 2020;9(5).
47. Butow PN, Lobb EA, Meiser B, Barratt A, Tucker KM. Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: a systematic review. *Med J Aust.* 2003;178(2):77-81.
48. Aspinwall LG, Taber JM, Leaf SL, Kohlmann W, Leachman SA. Genetic testing for hereditary melanoma and pancreatic cancer: a longitudinal study of psychological outcome. *Psycho-oncology.* 2013;22(2):276-289.
49. López-Fernández A, Villacampa G, Salinas M, et al. Role of psychological background in cancer susceptibility genetic testing distress: It is not only about a positive result. *Journal of genetic counseling.* 2023;32(4):778-787.
50. Culver JO, Ricker CN, Bonner J, et al. Psychosocial outcomes following germline multigene panel testing in an ethnically and economically diverse cohort of patients. *Cancer.* 2021;127(8):1275-1285.
51. Hirschberg AM, Chan-Smutko G, Pirl WF. Psychiatric implications of cancer genetic testing. *Cancer.* 2015;121(3):341-360.
52. Pichini A, Shuman C, Sappleton K, Kaufman M, Chitayat D, Babul-Hirji R. Experience with genetic counseling: the adolescent perspective. *Journal of genetic counseling.* 2016;25(3):583-595.
53. Bandura A. *Social Learning Theory.* Oxford, UK: Practice Hall; 1977.
54. Caes L, Goubert L, Devos P, Verlooy J, Benoit Y, Vervoort T. The relationship between parental catastrophizing about child pain and distress in response to medical procedures in

the context of childhood cancer treatment: a longitudinal analysis. *J Pediatr Psychol.* 2014;39(7):677-686.

55. van Oostrom I, Meijers-Heijboer H, Duivenvoorden HJ, et al. Experience of parental cancer in childhood is a risk factor for psychological distress during genetic cancer susceptibility testing. *Ann Oncol.* 2006;17(7):1090-1095.

Figure 1 PRISMA flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj

Table 1 Summary of empirical studies assessing the psychological impact of genetic testing in childhood cancer on children and parents

Author (year) Country	Quality Score (/100)	Sample, type of genetic condition	Study design, methods	Findings
1.Alderfer, Lindell, Viadro et al. (2017) USA	2.5/3	Adolescents (N=12) Age: 12-25y LFS Predictive + diagnostic testing	Qualitative Interview, descriptive content analysis approach	• All of the participants believed that genetic testing should be offered for children; but optional. • Half of the participants (N = 6) mentioned that knowing one's risk status, regardless of the result, allows one to prepare, reduces anxiety and increases one's power in the situation. • They personally did not experience negative emotions or felt that the negative emotions were transient. • The possibility of experiencing negative emotions is offset by the benefits or limited to individuals with a predisposition to worry. • They mention feeling nervous in advance. • The seriousness of having this (L)PV and the lifelong implications did not set in immediately. After a while it did and they accepted this fact. • A feeling of guilt because they don't have it. • They don't really feel that it's changed their sense of who they are or what they want to do with their life. • They accepted it and now some have a passion for life, some have always been like that but now probably more extreme.
2.Aspinwall, Stump, Taber et al. (2018)	3/3	Parents + adolescents (N = 114) Age: 16-69 y	Quantitative	• Feeling prepared to manage their risk. • Low negative emotions about melanoma risk.

USA		Unaffected members of melanoma-prone families, 65.8% with minor children or grandchildren CDKN2A (melanoma) Predictive testing	Longitudinal survey (1 month, 1 year after genetic counselling Measures: perceived costs and benefits of genetic counseling for management of melanoma risk inventory (self-administered)	• Carrier parents reported greater (but moderate) worry about their children's risk than no-test control parents. • Overall reports of negative emotions about melanoma risk were low at both assessments. • Carriers and no-test controls reported more negative emotions about their risk than non-carriers, but did not differ from each other. • Women reported more negative emotions about their risk than men. • Positive emotions: non-carriers reported greater hopefulness, relief and peace of mind about their risk than either carriers or no-test controls, carriers tended to report lower positive emotions about their risk than no-test controls. • Carrier parents reported significantly greater (though moderate) worry and discouragement about their children's risk than either noncarriers and no-test control parents. • No-test control parents reported greater worry than noncarrier parents. • Women indicated higher levels of worry than men.
3. Bon, Wouters, Hol et al. (2022) The Netherlands		Parents (N = 29) Renal tumors (WES-sequencing) Diagnostic testing	Qualitative Semi-structured interviews, Inductive thematic analysis	• Parents were generally positive about sequencing. • Families in which no predisposition was identified felt reassured. • Most families did not experience distress after a predisposition was disclosed, although sometimes stress following disclosure of a predisposition added to pre-existing (cancer-related) stress. • Drawbacks (if any) were outweighed by potential benefits. • The burden of sequencing was perceived as minimal. A minority

				indicated knowledge of having a genetic condition might induce stress. • Mixed feeling because nothing was found; it did not answer the questions they had about the cause of their child's tumor. • Parents of carrier-children were optimistic, focused on advantages of this knowledge, e.g. surveillance, use of reproductive techniques.
4.Codori, Petersen, Boyd et al. (1996) USA	2.4/3	Children + parents (N = 41 + parents) Age: 6-16y FAP Predictive testing	Quantitative Surveys before and 3 months after testing Measures: Children's Depression Inventory (CDI), Reynolds Adolescent Depression Scale (RADS), Revised Children's Manifest Anxiety Scale (RCMAS), Child Behavior Checklist (CBCL), Beck Depression Inventory (BDI)	• Children's depression, anxiety, behavior problem and competence scores remained in the normal range after testing. • Parents' depression scores remained within normal limits at follow-up. • (L)PV-positive children with affected mothers had significantly higher depression scores at follow-up. • Regardless of test results, children with affected mothers had significantly increased anxiety scores after testing. • In families with both (L)PV+ and (L)PV- children, FAP-unaffected parents experienced significantly increased depressive symptoms at follow-up. • (L)PV+ with affected fathers showed decreased depression scores at follow-up. • Regardless of the result, groups with affected fathers had a significant decrease in anxiety scores at follow-up. • The group with affected fathers showed fewer overall behavior problems than the groups with affected mothers.
5.Codori, Zawacki,	2.6/3	Children + parents (N = 48 + parents) Age: 5-17y	Quantitative Longitudinal Survey	• As a group neither the children nor the parents showed clinically significant psychological distress at any evaluation time point during 2-

Petersen et al. (2003) USA		FAP Predictive testing	Measures: Children's Depression Inventory (CDI), Reynolds Adolescent Depression Scale (RADS), Revised Children's Manifest Anxiety Scale (RCMAS), Child Behavior Checklist (CBCL), Beck Depression Inventory (BDI)	4 year follow-up. • Children who tested positive and had a (L)PV+ sibling showed significant, but subclinical, increases in depression symptoms. • Individual (L)PV- children with a positive sibling had clinical elevations in anxiety symptoms at one or more follow-ups. • (L)PV+ children with affected fathers had significantly decreased depression scores at the first and long-term follow-up. • Behavior problems decreased in all groups, children with affected fathers tended to show fewer behavioral problems than the children with affected mothers. • The anxiety scores for children with affected fathers, regardless of the test result, decreased at the first follow-up and remained low at the second follow-up, however, the scores at long-term follow-up were not significantly different from the baseline values. • Depression scores for (L)PV+ children with no positive siblings decreased significantly at long term follow-up. • (L)PV+ children with positive siblings had higher depression symptoms scores than (L)PV- children with no positive siblings. • (L)PV+ children whose mother had FAP had no statistically significant increases in depression scores at first follow-up.
6.Duncan, Gillam, Savulescu et al. (2008) Australia	2.2/3	Adolescents (N = 48 + parents) Age : 14-25y FAP	Qualitative In-dept interviews, content analysis and	• Witnessing distress in parents. • Experiencing a range of (unexpected) negative emotions : regret, guilt, stress (on the whole family), anxiety and lack of control while waiting

		Predictive testing	thematic analysis, grounded theory	for the result • Relief from uncertainty. • Witnessing relief in parents. • Feeling able to plan for the future (both in negative as in positive children). • Feeling empowered and experiencing a sense of clarity about what is important in life (both in negative as in positive children).
7.Forbes Shepherd, Werner-Lin, Keogh et al. (2021) Australia	2.8/3	Adolescents (N = 30) Age : 17-39y, mean = 25y LFS Predictive + diagnostic testing	Qualitative Semi-structured interviews, Interpretive description Inductive thematic analysis	• They opted for genetic testing to reduce uncertainty about gene status, but now experience a new uncertainty about living with a multi-organ cancer risk. • Decisional regret is not static, but can change over time.
8. Gjone, Diseth, Fausa et al. (2011) Norway	2.2/3	Adolescents (N = 22) Age: 11-20y FAP Predictive testing	Qualitative + quantitative Interview + questionnaires (cross-sectional) Measures : the Parental Account of Children's Symptoms (PACS), Chronic Family Difficulties (CFD), General Health Questionnaire (GHQ), Child Behavior Checklist (CBCL), Youth Self-	• 36% of the FAP offspring fulfilled criteria for a psychiatric diagnosis. • For ado's older than 15 years this was increased, relative to a comparison group. • Experiencing parental illness more than inheriting FAP is a perceived stressor for ado FAP offspring. • CFD, a score including illness in family members, was significantly associated with psychiatric diagnosis in the FAP sample. • Their own diagnostic situation, perception of illness severity, knowledge of cancer risk, experiencing genetic testing or age by

			Report (YSR), Child Assessment Schedule (CAS), Children's Global Assessment Scale (CGAS)	testing were not related to fulfilling criteria for a psychiatric diagnosis. • There was no difference in the occurrence of psychiatric diagnoses among those tested at birth compared to those tested later, (non-significant effect: better psychosocial functioning when tested earlier + also in the mothers). • According to the findings, late adolescence appears to be a more vulnerable period for FAP ado's than early adolescence.
9.Grosfeld, Beemer, Cornelis et al. (2000) The Netherlands	2.2/3	Parents (N = 47) MEN type 2 Predictive testing	Quantitative + qualitative Questionnaires + semi-structured interviews Measures : Impact of Event Scale (IES), Spielberger State Anxiety Inventory (STAI), Symptom Checklist 90 (SCL90), General Severity Index (GSI)	• Parents with carrier-children reacted with resignation, showed moderate to high levels of test-related and general anxiety, but few psychological complaints, daily activities were disturbed in 43% of the parents with carrier-children. • There was little disruption of the parents' future perspective, apart from some SES disadvantages and increased parental concerns for the carrier-children. • Parents with favorable test results showed significantly less anxiety and no disturbance in their daily activities. They did not, however, seem to be reassured by the DNA test result (combination of relieve, confusion and disbelief). • Parents, especially those with a lower level of education and/or a pessimistic view of the future, were distressed by unfavorable test results. • On one hand parents feel relieved to have some certainty, on the other

				hand, they showed concern for their children's health. • Parents who had more than one child tested and received both favorable and unfavorable test results reported significantly more general anxiety. • 82% of the parents with a favorable result felt that the quality of their lives would improve now they no longer had to worry about the onset of cancer in their children. • Parents own disease history showed no relationship with measures of distress.
10.Hill, Gedleh, Lee et al. (2018) Canada	2.5/3	Parents (N = 15) RB Diagnostic testing	Qualitative Focus groups Inductive thematic analysis	• Experiences with genetic testing and counseling were generally positive, however, participants reported challenges in accessing genetic information and psychosocial support. • Genetic testing providing benefits: ability to predict, helped allay some of the guilt for parents, relief. • Genetic testing comes at stressful time during diagnosis. • Experiencing guilt or feeling responsible for the development of RB in their child (more, when more generations are affected in the family). • Worry about secondary cancers.
11.Kattentidt-Mouravieva, den Heijer, van Kessel et al. (2014) The Netherlands	2.1/3	Parents (of 13 children) (N = 8) FAP Predictive testing	Qualitative Semi-structured interviews	• They felt more certain about the future. • Some felt that coping with uncertainty is more burdensome than coping with an unfavorable DNA result. • None of the parents observed changes in mental of physical health in their child after testing. • Genetic testing for FAP at a young age is experienced as causing no

				harm by patients.
12.Malek, Pereira, Robinson et al. (2019) USA	2.5/3	Parents (N = 64) Exome sequencing for solid tumors (not one specific genetic condition) Pre-test impact all + Post-test experience of (L)PV- Diagnostic testing	Qualitative Longitudinal semi-structured interviews (baseline + 1-8 months after result) Thematic qualitative analysis (inductive + deductive approach)	• Pre: they felt responsible for making the "right" choice. • Pre: Guilt and concern, that they had done something wrong. • Pre: afraid for blame from others for passing on a cancer susceptibility gene. • Pre: concerned about emotional impact. • Post: Feeling relieved of guilt and worry (even joy). • Post: they felt they had fulfilled parental duties by agreeing to genetic testing.
13.Malek, Slashinski, Robinson et al. (2017) USA	2.6/3	Parents (N = 64) Exome sequencing for solid tumors (not one specific genetic condition) Diagnostic testing	Qualitative Longitudinal interviews Thematic qualitative approach	• Peace of mind. • Relief of guilt. • Satisfaction of curiosity. • Disappointment when nothing was found as there is no explanation for the cancer development.
14.McGill, Wakefield, Vetsch et al. (2019) Australia	2.6/3	Parents + adolescents >16y (N= 35 = 26 + 9) not one specific genetic condition Diagnostic testing	Qualitative + quantitative Semi-structured interviews (inductive thematic analysis) + questionnaires Measures: Emotion Thermometers Tool (ETT), Genetic Counseling Satisfaction Scale (GCSS),	• Parents of children with cancer described the genetic consultations as a secondary concern to the immediate stressors of their child's treatment. • Parents felt reliefed when no (L)PV was found in their child (comfort, reassurance). • The proximal disease threat overshadows the long-term, it is what it is and you have to deal with it, the cancer treatment is more distressing (when (L)PV+ and affected), both for parents and child.

			Multidimensional Impact of Cancer Risk Assessment (MICRA), Quality of Life Patient/Cancer Survivor and Family Version (QoL-CSV, QoL-FV)	• Confronting to deal with as a parent when child is (L)PV+, but unaffected. • Guilt in parents. • Anxiety during testing period as parent. • Feeling isolated because of the rare condition, both in parents and child. • A found (L)PV made coping with cancer not harder. • No found (L)PV made coping with cancer not harder, but also not always easier.
15.Michie, Bobrow, Marteau (2001) UK	2.6/3	Adolescents (N = 60) 10-16y FAP Predictive testing	Quantitative Cross-sectional + prospective questionnaire Measures: Spielberger State Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS), Impact of Event Scale (IES), Rutter Child Behaviour Scale (RBS), Regrets (self-administered), Health Orientation Scale (HOS), Perception of Illness (self-administered), Life Orientation Test, Self-Esteem	• When receiving unfavorable results, mean scores for anxiety and depression were within the normal range (adults 43% clinical range). • But they were more anxious and depressed than those receiving favorable results (adults regardless of result, more anxious if low self-esteem and low in optimism). • Children are less anxious than adults. • Self-esteem increases after favorable test result.
16.Stump, Aspinwall,	2.5/3	Adolescents + mothers (N = 18 + mothers) 10-15y	Quantitative + qualitative	• Anxiety symptoms remained low post-disclosure, while depressive symptoms and cancer worry decreased.

Kohlmann et al. (2018) USA		CDKN2A/p16 (melanoma risk) Predictive testing	Longitudinal questionnaire + longitudinal interview Measures : Sun Habits Survey, Skin self-exam frequency (self-administered), Children's Depression Inventory-2 (CDI-2), Spielberger State Trait Anxiety Inventory-Children (STAI), Cancer worry (self-administered)	• It didn't make their children scared. • No participant approached clinical cutoffs for depression or anxiety at any point and no differences between carriers and noncarriers were observed. • Children generally reported that they did not think or worry about getting melanoma (61%). • Some children reported they are not really worried because they learned melanoma is treatable and that they can take steps to protect their skin. • Some are more scared of getting melanoma, but the degree of fear was not described in extreme terms. • Minors are not distressed following genetic counseling, although they seemed to understand their high-risk status. • Mothers: relief when no (L)PV was found.
17. Waldman, Hancock, Gallinger et al. (2022) Canada		Parents + adolescents (N = 45 = 22 + 10) (14-18y) (not all pairs) Next generation sequencing (all types of CPS) Diagnostic testing	Qualitative Semi-structured interviews, Inductive content analysis	• Low distress, no significant burden of added stress related to testing or results. • No anxiety while waiting for results, too busy with diagnosis and treatment. • Some expressed fear of the unknown, feelings of worry related to unveiling new or unexpected results. • Relief, comfort, and sense of control both in (L)PV+ and (L)PV-. • Empowered with knowledge. • Bringing closure and answering the question of why the cancer occurred.

				• Benefits and decisional satisfaction.
18.Weber, Shuman, Wasserman et al. (2019) Canada	2.6/3	Adolescents (N = 7) 14-17y Six differents CPSs Predictive + diagnostic testing	Qualitative Semi-structured interviews, Interpretive description	• Self-concept is influenced but not defined by tumor risk. • One adolescent who had not had a tumor suggested that knowing one's risk could support psychological adaptation in the event of tumor diagnosis. • Symptoms of anxiety and depression. • They felt concerned about uncertain penetrance for tumor development. • One participant expressed that he would have been upset if his syndrome had not been disclosed to him at the time that it was identified. • Difficult to watch family members coping with illness, and wondering if or when they may become ill themselves, difference between predictive and diagnostic testing. • Difference between familial mutation and de novo variant, they cannot share experiences. • They want to learn of one's CPS at an age old enough to understand it, but young enough to accept it and incorporate it into his/her life, they want to being able to grow up with this knowledge. • Frustration with limitations and burdens. • Participants look at the bright side and stated: it could have been worse.

Abbreviations: LFS (Li-Fraumeni syndrome), CDKN2A (cyclin-dependent kinase inhibitor 2A), FAP (Familial adenomatous polyposis), RB (Retinoblastoma), MEN type 2 (Multiple endocrine neoplasia type 2)

Table 2: Scientific merit scores of inluded studies

Included studies	Score S.V.H.	Score S.H.
Alderfer et al., 2017	2.5/3	2.3
Aspinwall et al., 2018	3/3	3
Bon et al., 2022	2.7/3	2.7
Codori et al., 1996	2.4/3	
Codori et al., 2003	2.6/3	
Duncan et al., 2008	2.7/3	2.8
Forbes Shepherd et al., 2021	2.8/3	2.8
Gjone et al., 2011	2.2/3	
Grosfeld et al., 2000	2.2/3	2.1
Hill et al., 2018	2.5/3	
Kattentidt et al., 2014	2.3/3	2.7
Malek et al., 2017	2.6/3	
Malek et al., 2019	2.5/3	
McGill et al., 2019	2.6/3	
Michie et al., 2001	2.6/3	
Stump et al., 2018	2.5/3	2.6
Waldman et al., 2022	2.5/3	2.6
Weber et al., 2019	2.6/3	