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Review Article

The impact of communicating uncertain test results in cancer genetic counseling: A systematic mixed studies review

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ABSTRACT

Objective: Cancer genetic counseling increasingly involves discussing uncertain test results, for example because multiple genes are sequenced simultaneously. This review was performed to provide insight into how counselors' communication of uncertain test results during genetic counseling for cancer affects counselors and counselees.

Methods: A systematic mixed studies review was undertaken to review research on the effects of communicating uncertain test results. Four databases were searched using a PICO search strategy. Study findings of articles meeting the inclusion criteria were synthesized narratively.

Results: Twenty-four articles were included. Uncertain test results encompassed either an inconclusive test result or a variant of unknown significance (VUS). Counselees involved almost exclusively women at risk of hereditary breast and/or ovarian cancer. None of the articles reported effects on counselor outcomes. Counselee outcomes were categorized as cognitive, affective or behavioral. Interpretation of a VUS was overall reported as difficult, and counselees' distress and worry were repeatedly found to decrease over time after the discussion of any uncertain test result. For most other outcomes, findings were sparse and/or inconsistent.

Conclusion: Evidence on effects on counselee outcomes is scant and inconsistent. Future studies are warranted to provide insight into how counselees and counselors are affected.

Practice implications: Clinical practice could benefit from guidelines on how to address uncertain test results during pre- and posttest genetic consultations.

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1. Introduction

Genetic counseling generally involves interpreting family and medical history, educating about inheritance, testing and prevention, and promoting informed decision making and adapting to the risk or condition [1]. Counselees (i.e. patients or their relatives) may seek genetic counseling to find out if they are genetically predisposed to developing cancer. Genetic counseling entails a pretest counseling session at which time large amounts of information are usually provided to counselees, for example about risks of developing cancer based on the counselee's medical and family history, and counselees are supported in their decision on whether or not to undergo genetic testing [1,2]. If a genetic test is carried out, a posttest counseling session usually takes place at which time the test result is disclosed and the consequences for the counselee and relatives are discussed [3,4].

Genetic test results generally involve the news that either a *pathogenic* variant or *no pathogenic* variant is found [5]. A *pathogenic* variant means that a permanent change is identified which causes a disease, e.g. cancer [6]. Counselees receiving this test result may develop the disease at some point in their life and are often referred to as carriers. In clinical practice, a *likely pathogenic* variant –a genetic variant with a high likelihood of being pathogenic– is nearly always treated as a *pathogenic* variant involving similar screening recommendations for counselees and their relatives [6]. The message that *no pathogenic* variant has been determined can, however, have various meanings. First, if the absence of a pathogenic variant known to be present in the family is confirmed, this is labelled a true-negative result. This outcome is often the result of predictive testing, i.e., pre-symptomatic testing to determine whether someone will develop a familial disease in the future (contrary to diagnostic testing to confirm whether the current disease is caused by a genetic predisposition) [7]. Counselees with a true-negative test result are often referred to as non-carriers. Second, the absence of a pathogenic variant may entail an absence without the guarantee that there is no genetic predisposition [8,9]. To some extent, this test result, often referred to as an inconclusive test result, is comparable to a true-negative result, except that it does not explain or provide certainty about why cancer runs in the family. In the case of an inconclusive test result, a genetic predisposition is suspected to exist in another gene than the one(s) currently tested. Therefore, uncertainty about carriership and the probability to develop cancer persists. Third, no proven pathogenic variant can also imply that a variant of uncertain significance (VUS) is determined. This means that the association with cancer and its implications are unknown [6]. Whether a VUS involves an increased risk to develop cancer and screening recommendations should be provided, is therefore uncertain for both counselors and counselees.

Hence, during genetic counseling, counselees do not exclusively receive certain test results as various test results involve uncertainty, for example about its association with cancer.

The incidence of uncertain test results, in particular of VUS, is rising. Amongst other, this is the result of technical advances, which increasingly enable simultaneous sequencing multiple cancer-associated genes, including less well-known genes [9,10]. Although there is consensus that uncertain test results should be discussed with counselees [11], guidelines in the Netherlands vary across genetic centers concerning to what extent to disclose such results. Moreover, counselors more often have to decide on an individual basis what screening and prevention options subsequently to provide to the counselee and his/her relatives [2]. Therefore, both counselors and counselees have to deal with uncertainty regarding these test results.

Discussion of uncertain test results does not only play a role during posttest counseling. To facilitate informed decision-making, the possibility of uncertain test results should preferably also be discussed with counselees during pretest counseling [1]. However, previous research has shown that counselors struggle with which uncertainties they should convey, including the extent to which they should a priori inform counselees about uncertain test results [12]. Moreover, a recent observational study indicated that counselors vary greatly in the extent and manner in which they discuss uncertain test results with counselees during pretest counseling concerning panel testing for hereditary cancer [13].

Literature shows that consensus and solid empirical evidence about the effects of communicating uncertainty in general is lacking [14]. Communicating uncertainty has been suggested to be beneficial as it enhances patient autonomy, helps them have more realistic expectations and enables informed decision-making [15,16]. However, enhanced awareness of uncertainty has also been shown to have the potential to overwhelm patients and increase their worries [16,17]. Unlike in other medical settings, counselors in clinical genetics are nowadays increasingly *required* to discuss uncertain test results with counselees [18]. This means that counselees are inevitably confronted with uncertainty. It is therefore crucial to know how this awareness of uncertainty affects counselees, as well as their relationship with the counselor who raises the issue of uncertainty. Possibly, *how* uncertainty is discussed determines its effects. Counselors may therefore learn from results regarding the effects of different communication styles and apply these to their own practice. At the same time, guidelines may be to counselors' own benefit as additional evidence suggests that counselors struggle with discussing uncertainty and may also be negatively affected by its discussion [12,19,20]. Counselors' confidence and ability in discussing uncertain test results might be enhanced when provided with some guidelines to ensure that counselees are adequately informed about uncertain test results before and after testing.

Yet, to meet the need for recommendations on how to discuss uncertain test results with counselees, we first need to know the effects thereof on counselors and counselees. We therefore performed a systematic review to answer the following research question: How does counselors' communication of uncertain test

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results during pre- and posttest genetic counseling for suspected hereditary cancer affect counselors and counselees cognitively, affectively and behaviorally?

2. Methods

2.1. Search strategy

Articles were searched focusing on [counselors providing genetic counseling for suspected hereditary cancer and counselees receiving this counseling] (Participants), [the communication of uncertainty] (Context and Intervention respectively), and [effects on counselor and counselee outcomes] (Outcomes) [21,22]. Assisted by a librarian (JD), four databases, *i.e.* Medline, Embase, PsycINFO and Web of Science, were systematically searched from inception until April 5, 2018 using the following terms: 'genetic counseling', 'uncertainty' and 'communication'. The PICO search strategy and a complete list of the search terms used in Medline is shown in Table 1.

2.2. Article selection and data extraction

Using the web app Rayyan [23], double screening of the titles and abstracts of all articles to check their eligibility was performed by two of three researchers (NM, LM and IP). The following types of articles were excluded: (a) editorials, reviews, or non-peer-reviewed articles, (b) articles not in Dutch or English, (c) articles not describing a face-to-face cancer genetic counseling session in a real clinical setting, and (d) articles not describing communication about uncertainty. Reference lists of the included abstracts were screened for additional articles. Next, the full texts of all remaining articles were read independently by two of three researchers (NM, LM and IP). During full-text screening, articles that did fulfil the following criteria were excluded: (a) articles for which the full-text was not retrievable, and (b) articles that did not report effects of communication of uncertain test results on counselor and/or counselee outcomes. In addition, the type of uncertain test result that was communicated had to be described in the methods section of the article. In the event of disagreement (n = 4), a senior reviewer (MH) was involved in the final decision regarding inclusion (see Fig. 1 for an overview of the article selection process). Data were extracted from all included articles by two researchers (NM and PvM) using a modified extraction form based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [24]. The effect(s) on counselor and counselee outcomes were registered as outcomes and categorized as cognitive (e.g. recall), affective (e.g. distress), and behavioral (e.g. screening behavior).

2.3. Synthesis of study findings

Conclusions about effects were based on a narrative synthesis of study findings [25]. This was done by; 1) developing an initial description of the findings (NM and PvM); 2) exploring patterns between study results and identifying factors that might explain differences in effects (NM and PvM); and 3) assessing the strength of the evidence for drawing conclusions and generalizing conclusions (NM) [25]. A narrative synthesis was chosen as our aim was to provide a summary of the current state of knowledge, and because it enabled us to synthesize a diverse body of research [25,26]. A meta-analysis was not feasible as studies used highly variable designs as well as measures [26].

2.4. Quality assessment

The study quality of included articles was independently assessed by two researchers (NM and PvM) to support the interpretation of the results. Assessments were discussed and disagreements were resolved at consensus meetings. Two validated checklists were used to assess study quality: the Newcastle-Ottawa Scale (NOS) for cross-sectional studies [27] adapted for quantitative studies, and the Critical Appraisal Skills

Table 1
PICO (21) and search terms for Medline.

	Participants	Intervention	Context[a]	Outcomes
PICO description	All counselors providing, and counselees receiving genetic counseling for suspected hereditary cancer	The communication of uncertainty[b]	Patient-provider communication	Effects on counselors' and counselees': 1. cognitive outcomes (e.g. perceived cancer risk and understanding) 2. affective outcomes (e.g. distress and confidence) 3. behavioral outcomes (e.g. decision making and ability to discuss uncertainty)
Search terms	Genetic counseling [MeSH] *Synonyms used for genetic counseling*: Genetic counsel* Genetic consult* Genetic assessment Genetic consult* Genetic test Genetic interact* Hereditary counsel* / assessment / consult* Inherited counsel* / assessment / consult* Familial counsel* / assessment / consult* Predispos* counsel* / assessment / consult*	Uncertainty [MeSH] *Synonyms used for uncertainty:* Uncertain* Doubt Ambigu* Probabilit*	Communication [MeSH] *Synonyms used for communication:* Communicat* Interpersonal communication Communicat* skill* Counseling Disclos* Message Conversat* Respond* Information provision Information exchange Providing information Decision making	No search terms were used

[a] Comparison/control was replaced by context as this was decided to be more suitable for this review.
[b] The initial search focused on uncertain information in general. During the process of article selection, it was decided to focus on uncertain test results in particular.

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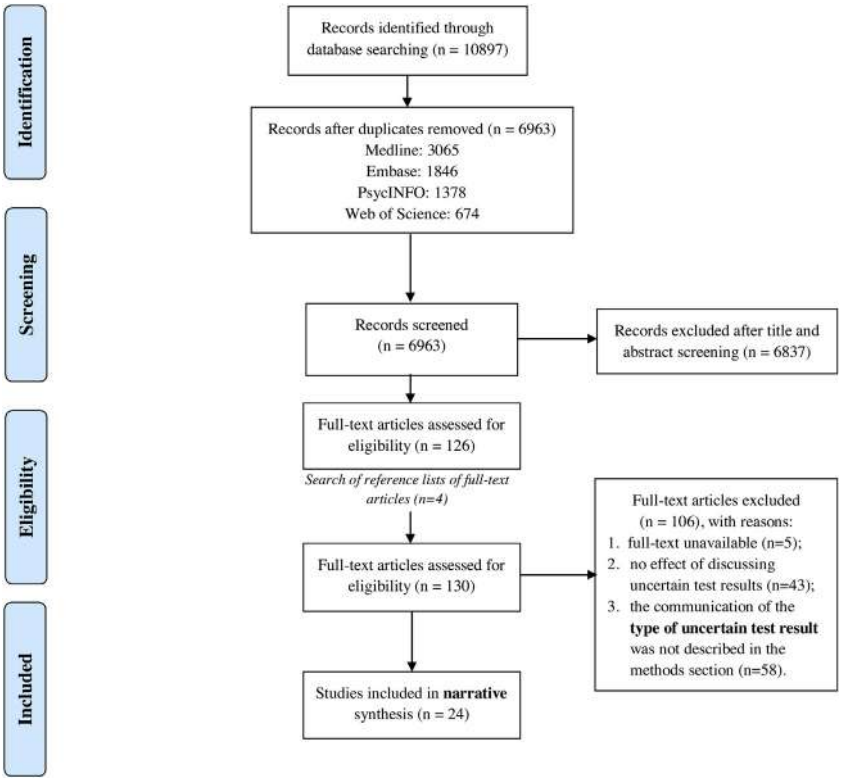

Fig. 1. PRISMA flow diagram visualizing the article selection process.

Programme (CASP) for qualitative studies [28]. The NOS contains eight items all of which can be scored with a maximum of two points. The CASP comprises ten items all scored with a maximum of two points. Total scores were divided by the maximum score to obtain percentages. The quality of studies with scores above 75 % was assessed as *high*, scores above 50 % as *moderate* and scores equal to or lower than 50 % as *low*.

3. Results

3.1. Article selection

After deduplication, the search yielded 6963 articles (see Fig. 1). After title and abstract screening, 126 articles remained. The reference lists of these articles were searched for additional hits resulting in four additional articles for full-text screening. Finally, 24 articles were included after full-text screening.

3.2. Included studies

3.2.1. Study characteristics

Four of the 24 included articles described qualitative studies. Of these four, two concerned interviews, one used an open-ended questionnaire, and one comprised both focus groups and interviews. The quantitative studies (n = 20) described cross-sectional (n = 6) and longitudinal research (n = 14), all using self-report questionnaires. Nineteen studies compared effects of discussing an uncertain test result with effects of discussing a certain test result (pathogenic variant and/or true-negative result). There were no experimental or intervention studies. Studies were performed between 2002 and 2018 in seven different countries: USA (n = 8), The Netherlands (n = 7), UK (n = 3), France (n = 3), Singapore, Canada and Spain (all n = 1). Table 2 shows key study characteristics of included articles in alphabetical order.

3.2.2. Study quality

NOS scores (quantitative studies) ranged from 53 %–88 %, and CASP scores (qualitative studies) ranged from 60 %–85 %. Of all studies, four quantitative and two qualitative studies were considered to be high quality. Sixteen quantitative and two qualitative studies were considered to be moderate quality. Tables 1a and 1b in the Supplement show full quality assessments of quantitative and qualitative studies, respectively.

3.2.3. Sample characteristics

None of the included articles reported outcomes for counselors. All but one study (n = 23) included counselees who attended to discuss their potential risk of carrying a predisposition for hereditary breast and/or ovarian cancer. The remaining study included counselees at risk of both hereditary breast and/or ovarian cancer and Lynch syndrome. In twenty-two studies, only women were included whereas the remaining two did not specify gender of participants. Sample sizes of quantitative studies ranged from 24 to 785, and of qualitative studies ranged from 15 to 30.

3.2.4. Communication of uncertain test results

Included articles only reported effects of the communication about uncertain test results during *posttest* counseling. Various terms were used to describe two types of uncertain test results: 1) test results that entailed identified variants of which the associated risks and consequences are unknown were referred to as either uncertain variants (UV) or variants of uncertain clinical significance (VUS or VUCS); and 2) negative test results (i.e. no variant had been identified) that do not guarantee the absence of a genetic predisposition were referred to as either uninformative negative results (UN or UR) or inconclusive test results. From now on, we will refer to these as VUS and inconclusive test results, respectively, to distinguish between them. Ten articles reported the effects of

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Table 2
Key characteristics of included studies (n = 24) in alphabetical order.

Author, year	Country	Design & methods	Sample characteristics	Type of uncertain test result	Cognitive outcomes	Affective outcomes	Behavioral outcomes
Bish et al., 2002 [29]	UK	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 6-month follow-up	Women (n = 63) with breast and/or ovarian cancer	Inconclusive test result	• Perceived cancer risk • Perceived risk of carrying a genetic predisposition	• Cancer distress and worry	• Intentions towards screening
Bredart et al., 2013 [44]	France	Design: Longitudinal Methods: Self-report questionnaires at pre- (T1) and post-counseling (T2)	Women (n = 273) with breast cancer	VUS and inconclusive test result *(vs a pathogenic variant)*	• Perceived risk of carrying a genetic predisposition (*at T1; as predictor for distress)*	• Distress (*at T2*)	
Bredart et al., 2017 [43]	France	Design: Longitudinal Methods: Self-report questionnaires at pre- (T1) and post-counseling (T2)	Women (n = 273) with breast cancer	VUS and inconclusive test result *(vs a pathogenic variant)*	• Knowledge (*at T1 and T2*)	• Distress	
Culver et al., 2013 [45]	USA	Design: Cross-sectional Methods: Self-report questionnaire at two year post-counseling	Women (n = 785) with a personal history of breast cancer	VUS and inconclusive test result	• Recall of cancer risk	• Cancer distress	• Surgical decisions
Cypowyj et al., 2009 [30]	France	Design: Longitudinal Methods: Self-report questionnaires at post-counseling and two year follow-up	Women (n = 30) with a personal and/or family history of breast cancer	Inconclusive test result	• Perceived cancer risk		• Family communication
Dorval et al., 2005 [31]	Canada	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling	Women (n = 535) with a family history of breast cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Perceived cancer risk	• Cancer worry • Quality of life • Relief	
Esteban et al., 2018 [39]	Spain	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 3- and 12-month follow-up	Patients (n = 187) at risk for hereditary breast and/or ovarian cancer or Lynch syndrome	VUS *(vs a true-negative result and a pathogenic variant)*		• Cancer distress and worry • Uncertainty • Positive experiences	
Frost et al., 2004 [46]	USA	Design: Qualitative Methods: Post-counseling focus group and interview	Women (n = 15) with breast cancer	VUS and inconclusive test result *(vs a pathogenic variant)*			• Family communication • Screening decisions
Hallowell et al., 2002 [32]	UK	Design: Qualitative Methods: Post-counseling interview	Women (n = 30) treated for breast and/or ovarian cancer	Inconclusive test result *(vs waiting for a result and a pathogenic variant)*	• Interpretation of test result	• Emotional responses (relief and disbelief)	• Family communication
Hanoch et al., 2014 [47]	UK	Design: Cross-sectional Methods: Self-report questionnaire at post-counseling	Unaffected women (n = 477) at increased risk for breast cancer based on family history	VUS and inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Interpretation of test result		
Kelly et al., 2008 [33]	USA	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 1 week and 6-month follow-up	Women (n = 78) at risk for hereditary breast and/or ovarian cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Perceived cancer risk		
Li et al. 2018 [40]	Singapore	Design: Qualitative Methods: Post-counseling interview	Women (n = 24) with a personal/family history of breast and/or ovarian cancer	VUS *(vs a true-negative result or a pathogenic variant)*			• Family communication
Lumish et al., 2017 [41]	USA	Design: Cross-sectional Methods: Self-report questionnaire at post-counseling	Counselees (n = 232) with a personal and/or family history of breast and/or ovarian cancer	VUS *(vs a true-negative result and a pathogenic variant)*	• Understanding of test result	• Distress • Satisfaction with decision • Discrimination	• Screening and treatment decisions

Table 2 (*Continued*)

Author, year	Country	Design & methods	Sample characteristics	Type of uncertain test result	Cognitive outcomes	Affective outcomes	Behavioral outcomes
O'Neill et al., 2009 [48]	USA	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 6- and 12-month follow-up	Women (n = 209) with a personal or family history of breast or ovarian cancer	VUS and inconclusive test result *(vs a true-negative result)*		• Cancer-specific and genetic testing distress	
Rini et al., 2009 [34]	USA	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 6- and 12-month follow-up	Women (n = 182) with a history of breast cancer	Inconclusive test result	• Decisional conflict		
Schwartz et al., 2002 [35]	USA	Design: Longitudinal Methods: Self-report questionnaires at pre-counseling and 6-month follow-up	Women (n = 279) with a personal and/or family history of breast and/or ovarian cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Perceived cancer risk	• Cancer-specific and general distress	
Schwartz et al., 2004 [49]	USA	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling	Women (n = 194), newly diagnosed with breast cancer	VUS and inconclusive test result *(vs a pathogenic variant)*			• Treatment decisions
van Dijk et al., 2004 [50]	The Netherlands	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling	Women (n = 241) who were referred for breast cancer counseling	VUS and inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Understanding • Perceived cancer risk	• Cancer-specific distress	
van Dijk et al., 2005 [36]	The Netherlands	Design: Longitudinal Methods: Self-report questionnaire at pre- and post-counseling	Women (n = 273) who received cancer genetic counseling for breast and/or ovarian cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Perceived risk of carrying a genetic predisposition		• Intentions towards screening
van Dijk et al., 2006 [38]	The Netherlands	Design: Longitudinal Methods: Self-report questionnaires at pre- and post-counseling and 1- and 7-month follow-up	Women (n = 762) with a personal and/or family history of breast cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*		• Cancer-specific distress and worry	
van Dijk et al., 2008 [37]	The Netherlands	Design: Longitudinal Methods: Self-report questionnaires at one and two year post-counseling	Women (n = 215) with a personal history of breast and/or ovarian cancer	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• Perceived risk of carrying a genetic predisposition	• Cancer-specific distress and worry • Uncertainty	
Vos et al., 2008 [42]	The Netherlands	Design: Qualitative Methods: Post-counseling interview	Women (n = 24) with breast and/or ovarian cancer	VUS	• Recall of test result • Interpretation and understanding of test result	• Treatment decision • Life changes	
Vos et al., 2011 [52]	The Netherlands	Design: Cross-sectional Methods: Self-report questionnaire at post-counseling	Women (n = 206) (un)affected with breast and/or ovarian cancer	VUS and inconclusive test result *(vs a pathogenic variant)*	• Recall • Interpretation of test result		
Vos et al., 2012 [51]	The Netherlands	Design: Cross-sectional Methods: Self-report questionnaire at post-counseling	Women (n = 206) (un)affected with breast and/or ovarian cancer	VUS and inconclusive test result *(vs a pathogenic variant)*	• Interpretation of test result • Perceived cancer risk	• Quality of life • Psychological well-being	

mmunication of inconclusive test results [29–38], and four of the communication of VUS [39–42]. The remaining ten articles reported effects of the communication of both types of uncertain test results [43–52].

3.3. Results regarding the effects of communicating uncertain test results

Ten studies reported results on either counselees' self-reported cognitive (n = 4), affective (n = 3) or behavioral outcomes (n = 3) only [33,34,38–40,46–49,52], whereas fourteen studies reported on multiple outcomes [29–32,35–37,41–45,50,51]. Reported cognitive outcomes were recall, interpretation, understanding and/or knowledge (n = 9), perceived cancer risk (n = 7), perceived risk of carrying a genetic predisposition (n = 5), and decisional conflict (n = 1). Affective outcomes included distress and worry (n = 12), quality of life (n = 2), uncertainty (n = 2), satisfaction (n = 2), feelings of relief (n = 2), experienced discrimination (n = 1), positive experiences (n = 1), and psychological well-being (n = 1). Finally, reported behavioral outcomes included family communication (n = 4), treatment decisions (n = 4), intentions towards screening (n = 2), and life changes (n = 2).

3.3.1. Cognitive outcomes

In total, eighteen studies reported how the discussion of uncertain test results affected counselees *cognitively* [29–37,41–45,47,50–52]. In Table 3, main results and quality assessment per study are shown for each cognitive outcome. Regarding recall and understanding, seven of the nine studies reported that, although recall was high [42,45,52], counselees' interpretation and understanding of a VUS was difficult or *incorrect* [41,42,45,47,50–52]. Only a few studies found that most counselees *correctly* interpreted a VUS [50] or understood an inconclusive test result [32]. Small differences were found in interpretation of a VUS when compared to an inconclusive test result (respectively 52 % and 45 % correct) [47]. Regarding counselees' genetic knowledge of breast cancer, a decrease was shown compared to before disclosure, and did not differ between groups [43].

Regarding risk perceptions, three of the seven relevant studies reported that counselees with whom an inconclusive test result was discussed perceived their risk of developing cancer as high, but that their perceived risk significantly *decreased* over time [29,35,50]. In contrast, two other studies reported counselees' perceived cancer risk to remain stable, similar to that of carriers [33], or to increase (simultaneously to an increase in accuracy of perception) [31]. For perceived cancer risk after the discussion of a VUS, one study reported it to remain stable [50]. Two studies, one of which was qualitative, reported on associations between counselees' perceived risk and other self-reported outcomes. The quantitative study reported that after the discussion of VUS or inconclusive test results, perceptions of high risk predicted high anxiety [44]. The qualitative study stated that of the counselees who received an inconclusive test result, those who believed they carried a mutation described a higher perceived risk compared with those who said they were unsure about their carrier status [30].

Three studies reported that counselee risk perception of carrying a genetic predisposition *decreased* after receiving an inconclusive test result, similar to the decreased risk perception of non-carriers [29,36,37]. Two of these studies additionally described that 6.6 % and 15 % of the counselees, respectively, who had an inconclusive test result *incorrectly* perceived their probability of carrying a genetic predisposition as nonexistent [36,37].In contrast, two studies reported that counselees with whom a VUS or an inconclusive test result was discussed were both found to inaccurately perceive their risk of carrying a mutation as being high [51]. Finally, a stronger negative association was found between perceived risk and levels of anxiety, depression and thought intrusion among counselees with a VUS than among counselees with an inconclusive test result or a pathogenic variant [44].

Regarding decisional conflict, one study reported that counselees with whom an inconclusive test result was discussed, had experienced difficulty in decision-making about risk management such as undergoing mammography, and experienced decisional conflict on the short-term, but not on the long-term [34].

To summarize, effects on five different cognitive outcomes were reported (see Table 6). Evidence on cognitive outcomes focused mostly on counselees' recall, interpretation and understanding, and perceived cancer risk and risk of carrying a genetic predisposition. The most consistent findings were that counselees had difficulty interpreting and understanding a VUS, and that perceived cancer risk and perceived risk of carrying a genetic predisposition decreased over time after the discussion of an inconclusive test result. For the remaining two cognitive outcomes, one study reported a decrease in knowledge after one of the uncertain test results, and another study reported short-term decisional conflict after an inconclusive test result (whereas a VUS was not studied).

3.3.2. Affective outcomes

In total, fourteen studies reported on the *affective* implications of discussing uncertain test results [29,31,32,35,37–39,41,43–45,48,50,51]. In Table 4, main results and quality assessment per study are shown for each affective outcome. Results of twelve studies on the associations between disclosure of uncertain test results and counselee distress and worry were contradictory [29,31,35,37–39,41,43–45,48,50]. In six studies, levels of distress and worry were reported to *decrease* shortly after the discussion of either a VUS or an inconclusive test result and in the long-term [31,37,38,45,48,50]. Contrary, one study reported an *increase* in distress after either one of these results [43], whereas other studies showed no significant change in distress over time in counselees with whom an inconclusive test result [29], or a VUS was discussed [39]. Studies comparing between test results reported a decrease in levels of distress and worry over time in counselees who had received a VUS, but higher levels than other test results (i.e. inconclusive, **pathogenic** and true-negative result) [41,45,48]. Conversely, one study reported no differences in distress scores between all groups [35]. Finally, one study reported that after being informed about a VUS, a lower perceived risk of carrying a mutation predicted higher scores for anxiety, depression and intrusion [44].

Two studies addressing quality of life (QOL) reported that, compared to counselees with an inconclusive test result, non-carriers more often perceived an improvement in QOL over time [31], and that an interpretation of a high cancer risk negatively predicted QOL in counselees with a VUS or an inconclusive test result [51].

No differences in levels of uncertainty between counselees with a VUS, non-carriers and carriers were found [39]. Another study showed that quite a few counselees with an inconclusive test result felt uncertain about their test result [37]. Furthermore, counselees with an inconclusive test result tended to be satisfied with the way in which they had been informed about their result [29]. For counselees being informed about a VUS, no difference in satisfaction with the decision to undergo genetic testing was found when compared with carriers or non-carriers [41].

Two studies looked at relief in counselees after the discussion of an inconclusive test result. Whereas the first study showed less relief in these counselees compared to non-carriers [31], the other, qualitative, study described how these counselees expressed various emotional responses, varying from relief to disbelief [32].

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Table 3
Overview of main study findings on *cognitive* outcomes and total scores of quality assessment (n = 18).

Author, year	Type of uncertain test result	Main results on cognitive outcomes	Study quality (NOS/ CASP)*
Vos et al. 2008 [42]	VUS	• **Recall and interpretation**: 67% correctly recalled a VUS as non-informative, and 79% interpreted it as carrying a mutation. Recall and interpretation were identical only in 7/13 persons. Women reported to have understood their result well.	75 % - Moderate (NOS)
Culver et al. 2013 [45]	VUS and inconclusive test result	• **Recall**: Approx. 75% of both groups could recall their breast cancer risk, whereas 56% could recall their ovarian cancer risk. Of those recalling their breast cancer risk and not being at high risk, 15% of VUS and 10% of counselees with an inconclusive test result believed they were at high risk ($p = .31$). Of those recalling their ovarian cancer risk and not being at high risk, 16% of VUS and 9% of counselees with an inconclusive test result recalled a high risk ($p = .29$).	62.5 % - Moderate (NOS)
Vos et al. 2011 [52]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Recall and interpretation**: Recall and interpretation of counselees with a pathogenic variant and a VUS differed significantly ($p<.01$), but not for an inconclusive test result. Interpretation of women with an inconclusive test result and a VUS was poorly predicted by recall; there were strong correlations and lack of differences between both recall and interpretations.	75 % - Moderate (NOS)
Lumish et al. 2017 [41]	VUS *(vs a true-negative result and a pathogenic variant)*	• **Understanding**: Four of the 14 counselees receiving a VUS correctly reported they had received a VUS and nine reported they had received a true-negative test result.	81.3 % - High (NOS)
Hanoch et al., 2014 [47]	VUS and inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Interpretation**: Women had difficulty interpreting a VUS and an inconclusive test result; 45% and 52%, respectively, correctly interpreted this result. They were likely to think that either they learned nothing from it, or they were as likely to develop cancer as the average woman.	75 % - Moderate (NOS)
van Dijk et al., 2004 [50]	VUS and inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Understanding**: Overall understanding of the information was high; women with a true-negative result reported the highest level and women with a VUS the lowest, although they did not differ significantly from women with a deleterious or an inconclusive test result. • **Perceived cancer risk**: Women with an inconclusive test result reported a decrease in perceived risk, whereas women with a VUS did not.	62.5 % - Moderate (NOS)
Vos et al., 2012 [51]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Interpretation**: VUS were inaccurately perceived; mostly overestimated. This misperception predicted both psychological outcomes and medical decisions. • **Perceived cancer risk**: Perception variables, especially interpreted cancer risks, predicted quality of life.	68.8 % - Moderate (NOS)
Hallowell et al., 2002 [32]	Inconclusive test result *(vs waiting for a result and a pathogenic variant)*	• **Interpretation**: The majority of women who had received an inconclusive result correctly understood its meaning, and a minority had misinterpreted it as a definitive confirmation that a predisposition was not present. Women expressed relief about them and their relatives not being at increased risk of developing cancer. Others said that they thought the news of not carrying a mutation, despite their family history, was an indication of inadequacy of the tests.	60 % - Moderate (CASP)
Bredart et al., 2017 [43]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Knowledge**: Mean knowledge decreased over time while not significantly differing between women with a VUS or an inconclusive test result.	86.7 % - High (NOS)
Bish et al., 2002 [29]	Inconclusive test result	• **Perceived cancer risk**: Perceptions of cancer risk decreased over time, with a significant reduction between pre- and post-result ($p<.05$), and no significant reduction between post-result and 6-month follow-up. • **Perceived risk of carrying a genetic predisposition**: Perceived risk of carrying a mutation also significantly decreased over time, with a significant reduction between pre- and post-result ($p<.001$), and a significant increase between post-result and 6-month follow-up ($p<.05$). Average perceived risk was still lower at 6-month follow-up than at pre-result ($p<.05$).	66.7 % - Moderate (NOS)
Schwartz et al., 2002 [35]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Perceived cancer risk**: For all groups, perceived cancer risk decreased. Groups did not differ on perceived cancer risk at both time points ($p<.61$ and $p<.10$, respectively).	68.8 % - Moderate (NOS)

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Kelly et al., 2008 [33]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Perceived cancer risk**: For all test results, perceived risk increased over time ($p = .027$). Risk accuracy for women with an inconclusive test result increased over time; from underestimation to overestimation, which was different than the increased accuracy among women with a pathogenic variant (decrease in underestimate) ($p = .06$) and the increased accuracy among women with a true-negative result (decrease in overestimate) ($p = .04$).	53.3 % - Moderate (NOS)
Dorval et al., 2005 [31]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Perceived cancer risk**: Among women whose test results were inconclusive or who had a pathogenic variant, perceived cancer risk remained stable between pre- and post-counseling compared to women with a true-negative result.	68.8 % - Moderate (NOS)
Cypowyj et al., 2009 [30]	Inconclusive test result	• **Perceived cancer risk**: 5 of the 7 women (71%) who were sure of carrying a pathogenic variant had high risk assessments; these were 55% and 57% for women being sure of not being a carrier and unsure about genetic status. Half of the group (7/14) who were unsure had a high risk perception compared with one of the seven women being sure about being carriers and two of the nine who were sure about not being carrier.	80 % - High (CASP)
Bredart et al., 2013 [44]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Perceived risk of carrying a genetic predisposition**: A higher perceived risk of a predisposition predicted higher levels of anxiety in women with a pathogenic variant compared with a VUS or an inconclusive test result ($p<.01$). Compared with women with an inconclusive result or who had a pathogenic variant, a higher perceived risk of a predisposition in women with a VUS predicted lower levels of anxiety ($p<.01$), depression ($p<.05$) and thought intrusion ($p<.05$). High risk perception predicted anxiety ($p<.01$).	87.5 % - High (NOS)
van Dijk et al., 2005 [36]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Perceived risk of carrying a genetic predisposition**: Comparable to a true-negative result, women with an inconclusive test result perceived the likelihood of carrying a predisposition as being significantly lower at post-counseling ($p<.0001$). Only 12 women with an inconclusive test result (6.6%) reported they had incorrectly concluded that the likelihood of carrying a mutation as being "nonexistent". One woman with an inconclusive test result incorrectly stated that she carried a pathogenic variant.	75 % - Moderate (NOS)
van Dijk et al., 2008 [37]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Perceived risk of carrying a genetic predisposition**: Of the women with an inconclusive test result, 15% reported that there was no personal risk of carrying a predisposition.	75 % - Moderate (NOS)
Rini et al., 2009 [34]	Inconclusive test result	• **Decisional conflict**: Many women receiving an inconclusive test result reported experiencing difficulty in decision-making about risk management behaviors and experienced decisional conflict. There was a reduction in decisional conflict from post-counseling to 12-month follow-up ($p<.004$).	80 % - High (NOS)

* The Newcastle-Ottawa Scale (NOS) was used for quantitative studies (27) and the Critical Appraisal Skills Programme (CASP) for qualitative studies (28). Maximum score of NOS is 16, and of CASP is 20. Total scores of studies were divided by the maximum score to obtain percentages. Study quality was assessed as following: >75 % as high, >50 % as moderate; ≤50 % as low.

Finally, only one study per outcome was found that reported on the effects of the communication of a VUS on counselee experience of discrimination, their positive experiences and psychological well-being. Counselees reported fear of being discriminated against based on their test results; two counselees had actually experienced discrimination when trying to take out an insurance policy [41]. Counselees with whom a VUS had been communicated had lower levels of positive experiences than non-carriers [39], and a misperception of high risk regarding VUS predicted decreased psychological well-being in this group [51].

In sum, eight different affective outcomes on which effects were reported were identified. Most studies describing affective outcomes of communicating uncertain test results reported on counselees' distress and worry. Counselees' distress and worry were rather consistently found to decrease over time, regardless of which uncertain test result was discussed. Levels of distress and worry in counselees receiving a VUS were consistently found to be comparable to or higher than levels in counselees receiving other test results (certain and uncertain). Effects on other affective outcomes, i.e. quality of life, uncertainty, satisfaction, relief, experience of discrimination, positive experiences, and psychological well-being, were either contradictory, incomplete or reported in singular studies (see Table 6). Thus, no general conclusions can be drawn on the effects of communicating uncertain test results on affective outcomes other than distress and worry.

3.3.3. Behavioral outcomes

In total, ten studies reported how the discussion of uncertain test results affected counselees *behaviorally* [29,30,32,36,40–42,45,46,49]. In Table 5, main results and quality assessment per study are shown for each behavioral outcome. How counselees experienced family communication was only reported on by qualitative studies [30,32,40,46]. Contradictory findings were described concerning counselees with whom an inconclusive test result was discussed [30,32]. One study described that counselees expressed difficulties in informing relatives [30], whereas other

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Table 4
Overview of main study findings on *affective* outcomes and total scores of quality assessment (n = 14).

Author, year	Type of uncertain test result	Main results on affective outcomes	Study quality (NOS/ CASP)*
Dorval et al., 2005 [31]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Cancer worry:** Comparing women with an inconclusive and a true-negative result 39% and 64%, respectively reported being less worried about cancer than before receiving their result. • **Quality of life:** Finally, 14% and 22% respectively, perceived an improvement of their quality of life post-counseling (all $p<.0001$). • **Relief:** 61% and 80%, respectively, felt moderate or great relief following the result disclosure.	68.8 % - Moderate (NOS)
van Dijk et al., 2008 [37]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Cancer-specific distress and worry:** Cancer-specific distress and worry scores at post-counseling were lower than before counseling for women with an inconclusive test result ($p<.0001$ and $p<.001$ respectively). Women with an inconclusive result and a pathogenic variant had highly comparable scores on distress. • **Uncertainty:** Quite a few women with an inconclusive test result were uncertain about their test result: more uncertainty was associated with higher distress and lower adjustment.	75 % - Moderate (NOS)
van Dijk et al., 2006 [38]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Cancer-specific distress and worry:** Women who received an inconclusive result reported a lower level of worry ($p<.001$) and distress ($p<.001$) at 1 month post-counseling, which remained stable up to 7 months. At 7 months, women with an inconclusive test result at low risk reported similar low levels of worry and distress as women with a true-negative result ($p = .46$ and $p = .53$ respectively), whereas women with a high risk had comparable to distress of women with a pathogenic variant ($p = .16$). The latter had higher worry levels than women with an inconclusive test result ($p<.034$).	75 % - Moderate (NOS)
Culver et al., 2013 [45]	VUS and inconclusive test result	• **Cancer distress:** The VUS group reported less cancer distress reduction than the group with an inconclusive test result ($p<.043$).	62.5 % - Moderate (NOS)
O'Neill et al., 2009 [48]	VUS and inconclusive test result *(vs a true-negative result)*	• **Cancer-specific and genetic testing distress:** Anxiety and depression scores of women receiving a VUS stayed stable between pre- and post-counseling and 6-month follow-up and then decreased to 12-month follow-up ($p<0.01$). Women with a VUS had higher anxiety and depression scores at the post-counseling and 6-month follow-up than other women ($p<.01–.07$). Cancer-specific distress only marginally declined from pre- to post-counseling for women with VUS, compared to others. Genetic testing distress remained stable over time for women with VUS. Women with VUS had higher genetic testing distress than the other groups at all-time points ($p<.001–.05$).	68.8 % - Moderate (NOS)
van Dijk et al., 2004 [50]	VUS and inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Cancer-specific distress:** Women with a true-negative result reported the lowest level of distress after test disclosure ($p<.0001$). A similar level of distress before and after test disclosure was reported for women with a pathogenic variant, whereas women with a VUS and inconclusive test result reported a decrease in level of distress.	62.5 % - Moderate (NOS)
Bredart et al., 2017 [43]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Distress:** Receiving a VUS or a pathogenic variant significantly increased the level of distress.	86.7 % - High (NOS)
Bish et al., 2002 [29]	Inconclusive test result	• **Cancer distress and worry:** No changes in psychological distress and worry were reported after having received an inconclusive test result.	66.7 % - Moderate (NOS)
Lumish et al., 2017 [41]	VUS *(vs a true-negative result and a pathogenic variant)*	• **Distress:** Impact of event and distress scores were highest among patients with a pathogenic variant. Distress scores were higher in the VUS group compared with the true-negative group ($p<.03$). • **Satisfaction:** There was no significant difference in satisfaction with the decision to undergo genetic testing between groups. • **Discrimination:** More patients reported worrying about discrimination based on their genetic test results than had actually experienced discrimination. Two patients with a VUS reported problems with trying to take out an insurance policy.	81.3 % - High (NOS)

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Schwartz et al., 2002 [35]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Cancer-specific and general distress:** Groups did not differ on change in cancer-specific distress ($p = .78$) or general distress ($p = .52$).	68.8 % - Moderate (NOS)
Esteban et al., 2018 [39]	VUS *(vs a true-negative result and a pathogenic variant)*	• **Cancer distress and worry:** Cancer worry scores and impact of event scores did not change significantly over time, and did not differ between groups. • **Uncertainty:** Patients receiving news of a pathogenic variant had higher levels of distress than patients receiving a true-negative result or a VUS ($p<.01$). No differences were found in the levels of uncertainty at the 3 time points between groups. • **Positive experiences:** Patients with a true-negative result showed higher levels of positive experiences than patients with a VUS and a pathogenic variant.	75 % - Moderate (NOS)
Bredart et al., 2013 [44]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Distress:** In women receiving a VUS (vs an inconclusive result or a pathogenic variant), a lower perceived probability of cancer genetic predisposition than objective estimates at T1 predicted higher levels of anxiety, depression and intrusion at T2.	87.5 % - High (NOS)
Vos et al., 2012 [51]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Quality of life:** An interpretation of a high cancer risk negatively predicted QOL in counselees with a VUS and an inconclusive test result. • **Psychological well-being:** A misperception of a high risk regarding a VUS predicted decreased psychological well-being in women receiving a VUS.	68.8 % - Moderate (NOS)
Hallowell et al., 2002 [32]	Inconclusive test result *(vs waiting for a result and a pathogenic variant)*	• **Emotional responses:** Women receiving an inconclusive test result reported a range of emotional reactions, varying from relief or even elation and disbelief, through acceptance to disappointment and anger or frustration. Some of these women expressed other negative emotions such as anger, shock, and frustration that they did not obtain a conclusive answer about their family history of cancer.	60 % - Moderate (CASP)

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studies described that all counselees shared their results with family and friends [46], or did not experience difficulties in conveying information, compared to carriers [32]. The latter study additionally reported that counselees argued that they did not have to break bad news of a pathogenic variant. In addition, counselees with whom a VUS was discussed also indicated to have shared their test result with family and friends [46]. Finally, one study compared the discussion of a VUS with a pathogenic variant and a true-negative result, and pointed out that all groups delayed or waived sharing their result if they believed it to be a mental or emotional burden to relatives [40]. Moreover, counselees with a VUS had difficulty converting it into meaningful information, and preferred to avoid misunderstanding or to creating false alarm [40].

Treatment decisions (i.e. mastectomy vs breast-conserving therapy) were found not to differ between counselees receiving a VUS and those receiving an inconclusive test result [45], or between counselees receiving a VUS and carriers and non-carriers [41]. Another study, however, reported that carriers were significantly more likely to choose mastectomy whereas counselees receiving an inconclusive test result more frequently chose breast-conserving therapy [49]. A qualitative study on the effects of receiving a VUS reported that most women said they had undergone mastectomy because of their test result [42]. The percentage of counselees receiving a VUS who reported to increase their screening frequency was higher than that of counselees receiving a pathogenic variant or true-negative result: 21.4 % vs 9.1 % and 15.4 % respectively [41]. According to two studies, *intention* to be screened among those receiving an inconclusive test result was reported to be already high and did not change after test disclosure [29,36].

Lastly, most counselees with a VUS reported that receiving this test result had changed their lives little, whereas 25 % mentioned large life changes [42]. Women participating in a qualitative study, receiving either one of the uncertain test results, indicated they believed that having cancer had more impact on their behavior than receiving their test result [46].

To conclude, evidence on the effects of communicating uncertain test results on counselees' behavior mainly regarded information dissemination within families and treatment decisions (see Table 6). Findings were highly inconsistent for both outcomes, preventing any firm conclusions. For two other identified behavioral outcomes, i.e. intentions towards screening and life changes, studies mainly reported that both outcomes hardly changed after the discussion of one of the uncertain test results.

4. Discussion and conclusion

4.1. Discussion

In this systematic mixed studies review, twenty-four articles were identified that investigated effects of communicating a VUS and/or an inconclusive test result on counselee outcomes; none of the reviewed studies reported results on counselor outcomes. Studies almost exclusively examined effects on women at risk for breast and/or ovarian cancer. Findings were inconsistent on how counselees are affected in terms of their cognitions, their affective reaction and/or their behavior, which complicates drawing conclusions. Several counselee outcomes were assessed in one study only. Even for outcomes assessed in multiple studies aggregating results was problematic because of strong

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Table 5
Overview of main study findings on *behavioral* outcomes and total scores of quality assessment (n = 10).

Author, year	Type of uncertain test result	Main results on behavioral outcomes	Study quality (NOS/ CASP)*
Cypowyj et al., 2009 [30]	Inconclusive test result	• **Family communication:** Women sure of not carrying a predisposition expressed to feel no hesitation about conveying (or not conveying) this information to their families; most said they had informed their relatives. Women unsure about being a carrier said to find it difficult to explain the issue to their relatives. The majority of women who were sure about being a carrier transmitted information to their relatives assuming that they have to comply with screening recommendations.	80 % - High (CASP)
Hallowell et al., 2002 [32]	Inconclusive test result *(vs waiting for a result or a pathogenic variant)*	• **Family communication:** Unlike carriers, most women in the inconclusive group did not report experiencing problems in disclosing inconclusive test results to relatives. The argued that they did not have to break bad news as their test result did not change their relatives' risk status.	60 % - Moderate (CASP)
Li et al., 2018 [40]	VUS *(vs a true-negative result or a pathogenic variant)*	• **Family communication:** All participants showed willingness to disclose their results to relatives. Similar to carriers, willingness of women receiving a VUS to disclose their result decreased when there was no future action to take. In addition, this group reported difficulty in converting a VUS into meaningful information, and therefore preferred not to share it with their relatives to avoid misunderstanding and creating "false alarm".	85 % - High (CASP)
Frost et al., 2004 (46)	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Family communication:** Women from all groups had alerted family members. Some family members of women with a VUS were unclear about the meaning of the results. • **Screening decisions:** Women with a VUS or inconclusive test results believed that the cancer impacted them and their screening decisions long before the test results were available to them.	75 % - Moderate (CASP)
Culver et al., 2013 [45]	VUS and inconclusive test result	• **Surgical decisions:** Surgical decisions did not differ between the two groups ($p>.1$).	62.5 % - Moderate (NOS)
Lumish et al., 2017 [41]	VUS *(vs a true-negative result and a pathogenic variant)*	• **Screening and treatment decisions:** Groups did not differ in treatment decisions. 21.4% of the patients with VUS reported that their result affected their decision for additional or more frequent screening.	81.3 % - High (NOS)
Vos et al., 2008 [42]	VUS	• **Treatment decisions:** Counselees receiving a VUS stated to have undergone mastectomy because of their test result. • **Life changes:** Most women reported that their test result changed their lives little, and 25% reported large life changes. Existential view on life and risk management changed the most.	75 % - Moderate (NOS)
Schwartz et al., 2004 [49]	VUS and inconclusive test result *(vs a pathogenic variant)*	• **Treatment decisions:** Overall, women with a pathogenic variant were significantly more likely to choose bilateral mastectomy (48%) compared with women with a VUS or an inconclusive test result ($p<.001$). 77% of the 129 women waited for their result before proceeding with surgery, surgical decision was strongly associated with test result ($p<.004$). In this group, 52% of the women carrying a mutation opted for bilateral mastectomy, compared with 24% with a VUS or an inconclusive test result.	75 % - Moderate (NOS)
Bish et al., 2002 [29]	Inconclusive test result	• **Intentions towards screening:** No changes were reported in intentions to have mammograms or to carry out breast self-examination more frequently, nor in intentions to have a mastectomy or oophorectomy, with intentions remaining high.	66.7 % - Moderate (NOS)
van Dijk et al., 2005 [36]	Inconclusive test result *(vs a true-negative result and a pathogenic variant)*	• **Intentions towards screening:** Women with a pathogenic variant and an inconclusive result did not change their screening intention after disclosure. 151 out of 173 (87%) of the latter group reported a positive intention towards mammography. The 12 women who incorrectly interpreted their result as being carrier, reported they intended to have at least annual mammograms.	75 % - Moderate (NOS)

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methodological variations, for example in measurement instruments and timing. A more systematic research approach is warranted. This may, among others, be accomplished when different studies use similar measurement instruments. Examples are the Psychosocial aspect of hereditary cancer (PAHC) questionnaire or Genetic Counseling Outcome Scale (GCOS), which have been developed to measure patient outcomes in the genetic setting particularly [53,54]. Also, most studies were descriptive, which prevents conclusions about the causal effects of communicating uncertain test results. Intervention and experimental studies are needed to identify causality, for example by using a video vignette design [55]. Furthermore, although no 'low-quality' studies were included in this review, only few studies were rated as high quality. Several outcomes were only examined in a single study of moderate quality; results from these individual studies cannot be readily extrapolated. Other outcomes were examined by multiple studies, some of which were of moderate and others were of high quality. This further complicates comparing and weighing results.

Closer inspection of how discussing a VUS *vs.* an inconclusive test result may affect counselees differently, indicated that the two often generate separate effects (Table 6). We tentatively conclude that discussing an inconclusive test result affects counselees less negatively than a VUS. This might be explained by the nature of both types of uncertain test results. Counselees may be used to situations in which they can only be preliminarily reassured, like when receiving an inconclusive test result. The medical setting often involves situations in which guarantees about health cannot be given, for example when undergoing periodic screening [56]. Subsequently, counselees may be able to tolerate a message indicating that nothing has been found *so far*. VUS, on the other hand, are still a relatively new phenomenon [10]. Counselors may not yet be completely used to handling and communicating the complex ambiguities associated with a VUS [57], and may therefore not optimally convey this information. Besides, it is likely that inconclusive test results are discussed in a more reassuring way, i.e. saying that for now no predisposition is found, and merely warning that, in rare cases, this changes depending on future developments. In contrast, explicitly stating that someone is carrier of a variant but that, at the same time, there is uncertainty about the meaning and implications thereof, may be perceived by counselees as being more uncertain and difficult to grasp or act upon [10]; they may even perceive the identification of a VUS as a deleterious variant [58].

Personality differences between counselees and their individual preferences may influence how they are personally affected by the discussion of uncertain test results. Particularly, counselees' tolerance of uncertainty may impact the extent to which they are affected by it [59]. However, in none of the included studies, counselees' uncertainty tolerance was assessed. Differences in counselees' information preferences may explain why some studies did not find effects on cognitive and emotional outcomes: a previous review indicated that counselees' need for cancer-focused, personalized information was not always met by genetic counseling, subsequently affecting their cognitive and emotional outcomes [60]. This could imply that, in the included studies, counselees' cognitive and emotional outcomes were impacted by the counseling as a whole, rather than by the discussion of uncertain test results specifically [60,61]. Furthermore, *how* counselors communicated uncertain test results may vary and may therefore have generated different effects on counselees' outcomes [62]. None of the included articles provided information on the manner in which the results were communicated. It is therefore still a black box whether and how the manner of providing uncertain test results contributed to the outcomes described in the reviewed studies. In clinical practice, counselors may also differ in the way in which they communicate uncertain test results and how they support counselees in dealing with this uncertainty [63,64]. Further research is needed to establish if it is detrimental to communicate uncertain test results, and if so, whether and how the manner of communication impacts its effects. The current results imply that communicating uncertain test results is not by definition harmful for counselees. It is also conceivable that addressing test related uncertainty can be beneficial, as it enhances counselees' autonomy, may lower pessimistic risk perceptions and subsequently provide hope, and enables informed decision-making [15,16]. By using specific communication strategies, such as positive talk and partnership building, a negative impact can be prevented and positive coping strategies can be encouraged [16,65,66]. For this reason, it would be valuable to examine not only the possible harmful effects, but also the possible beneficial effects of uncertainty disclosure on counselee outcomes, such as feelings of hope or perceived honesty of the clinician. Such outcomes were hardly reported on in the studies included in our review.

No articles were identified that studied the association between the communication of uncertain test results and counselor outcomes. Yet, it would seem essential to gain insight into how they are affected as they seem to struggle with the extent to which they need to communicate uncertain information regarding test results in genetic consultations [12,67]. Counselors may be emotionally affected by the felt pressure of discussing uncertain test results [59]. Their sense of emotional burden may depend on how well they are able to understand and interpret uncertain test results [8]. Counselors' emotional reaction may subsequently influence whether and to what extent they discuss uncertain test results with counselees, feel able to explain this information in a comprehensive way, and are able to deal with counselees' questions and emotions. The impact of uncertain test results may also vary between counselors depending on their need for control and uncertainty tolerance. It has been shown that physicians with lower uncertainty tolerance are less likely to communicate uncertainties [59], which in turn affects the degree to which patients are informed. The interplay between counselors' perceptions of uncertain test results, their communication and their tolerance of uncertainty should be investigated. Eventually, interventions may be required to ensure that all counselees are adequately informed about their test result irrespective of which counselor they see [68].

We did not identify any studies that examined the effects of communicating uncertain test results during *pretest* counseling. This is problematic in the light of decision making: to enable counselees to make informed decisions about whether or not to proceed with testing counselees need to know beforehand that a genetic test may generate uncertain results. This is particularly important considering the increased use of multigene panel tests, which commonly yield uncertain test results. No studies included in our review specified whether uncertain test results resulted from multigene panel tests; in fact, most articles pre-dated panel testing. In the future, multigene panel tests and the associated potential uncertain test results may increasingly be discussed during *pretest* counseling to inform counselees comprehensively and enable them to decide about whether to pursue with testing. More evidence is therefore necessary on how discussing these uncertainties during *pretest* counseling affects counselees and the decision making process. This may guide counselors in how to address uncertain test results and help counselees deal with these.

Articles included in this review almost exclusively described results on counselees at risk for hereditary breast and/or ovarian cancer. As a result, almost exclusively female counselees participated, which raises the question of effects on outcomes in men. Furthermore, as breast cancer is the most common form of cancer

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Table 6
Summary of findings for each *cognitive, affective* and *behavioral* outcome separately for VUS and inconclusive test result.

	Uncertain test result	
Cognitive outcomes	**VUS**	**Inconclusive test result**
Recall, interpretation and/or understanding	7 out of 9 studies reported that counselees' recall was high but interpretation and understanding was difficult.	No uniform results were found regarding the interpretation of test results: both high and moderate levels of interpretation were found.
Knowledge	*For both VUS and inconclusive test result:* One study reported that counselees' knowledge decreased, regardless of the uncertain test result received.	
Perceived cancer risk	One study found that counselees' risk perceptions remained stable over time.	Three studies reported that counselees' risk perceptions were high but decreased over time; one reported risk perceptions to increase and one to remain stable.
Perceived risk of carrying a genetic predisposition	One study reported that counselees inaccurately perceived risk of a VUS as high.	Three studies reported a decrease in counselees' perceived risk of carrying a predisposition, whereas one study reported that risk was inaccurately perceived as high.
Decisional conflict	n.a.[a]	One study reported counselees to experience decisional conflict about risk management on the short term.
Affective outcomes	**VUS**	**Inconclusive test result**
Distress and worry	*For both VUS and inconclusive test result*: 6 out of 8 studies reported a decrease in counselees' distress and worry on the short and long term after the discussion of an uncertain test result. Both similar and higher levels of distress after a VUS were found compared to other test results, whereas studies did not provide information on distress levels for inconclusive test results.	
Quality of life	One study reported that counselees receiving a VUS and who interpreted their cancer risk as higher had a lower quality of life.	One study reported that compared to non-carriers, counselees with an inconclusive test result were less likely to experience an improvement in their quality of life. Another study described that counselees receiving an inconclusive test result and who interpreted their cancer risk as higher had a lower quality of life.
Uncertainty	One study reported no differences in levels of uncertainty between counselees with a VUS and (non-)carriers.	One study reported that feelings of uncertainty were common in counselees receiving an inconclusive test result.
Satisfaction	One study reported that compared to carriers and non-carriers, counselees with a VUS were equally satisfied with their decision to undergo testing.	One study reported that counselees receiving an inconclusive test result were highly satisfied about how they were informed.
Relief	n.a.	One study reported less relief among counselees receiving an inconclusive test result compared to non-carriers.
Experience of discrimination	One study reported that counselees receiving a VUS experienced (fear of) discrimination.	n.a.
Positive experiences	One study reported that counselees receiving a VUS had lower levels of positive experiences compared to non-carriers.	n.a.
Psychological well-being	One study reported that counselees receiving a VUS who had a misperception of high risk had lower psychological well-being.	n.a.
Behavioral outcomes	**VUS**	**Inconclusive test result**
Family communication	One study reported that counselees waved or delayed conveying a VUS to family members when they suspected emotional burden in relatives or wanted to avoid misunderstanding.	Results of two studies were contradictory regarding difficulties with family communication.
Treatment decisions and/or screening frequency	One study reported counselees receiving a VUS did not differ in treatment decision compared to counselees receiving other test results, yet screening frequency was higher for counselees receiving a VUS. Another study reported that this group of counselees more frequently opted for breast-conserving therapy compared to carriers.	One study reported that counselees receiving an inconclusive test result more frequently opted for breast-conserving therapy compared to carriers.
Intentions towards screening	n.a.	Two studies reported that counselees' intentions to undergo screening were already high and did not change afterwards.
Life changes	One study reported that counselees in this group primarily described little as well as large life changes, and stated that these changes were due to cancer instead of their test result.	One study reported that counselees stated that life changes were due to cancer instead of their test result.

[a] No results were found.

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[69], it is the main reason for counselors to perform genetic counseling for cancer [2]. Counselors' wide experience with counseling about hereditary breast and/or ovarian cancer in particular, may have positively influenced their skills and the manner in which they communicate. It would be interesting for future research to examine if discussion of uncertain test results, and the outcomes thereof, are affected by type of cancer and counselees' gender.

4.1.1. Strengths and limitations

A strength of this review is our broad search strategy to identify all articles reporting effects of communicating uncertainty during genetic counseling. Moreover, we only included articles describing in the methods section the type of uncertain test result that was communicated during genetic counseling. This led to the exclusion of articles only suggestively describing that an uncertain test result was communicated. This enabled us to identify the specific types of uncertain test results and their effects. However, as a result we may have missed articles describing the effects of communicating uncertain test results without specifying the type of results. Relatedly, as mentioned, most of the reviewed studies pre-dated multigene panel testing. A final limitation of our review is that only articles in English or Dutch, and for which full text was retrievable were included.

4.2. Conclusions

This systematic mixed studies review provides an overview of the literature on how the communication about uncertain test results may affect counselees during cancer genetic consultations. Articles reported effects on several different cognitive, affective and behavioral outcomes of counselees. Partly due to varying methodologies, few consistent results were found. We encourage future studies to gain more knowledge about the effects of imparting information that is uncertain, such as test results that do not provide a definitive answer, since such information is an intrinsic aspect of genetic counseling.

4.3. Practice implications

To provide practical recommendations for communication skills training and clinical practice, more research on the effects of communicating uncertain test results is warranted. First, the variable effects of communicating uncertain test results we found, may at least partly be explained by differences in counselors' communication styles. Studies on *how* uncertain test results are communicated, i.e. the communicative strategies used by counselors, are highly needed to examine if and how manners of communication are influencing how counselees are affected. Second, we suggest that future research systematically compares the effects of different types of uncertain test results, as this may reveal if and how counselees are affected by its discussion. Eventually, this should culminate into practical guidelines for counselors on how to address uncertain test results during pre- and posttest genetic consultations as well as how to tailor their communication to counselees, taking counselees' individual differences into account. Third, studies are needed to reveal how communicating uncertain test results affects counselors. Still, the results of this review suggest that communicating uncertain test results with counselees during cancer genetic counseling is not necessarily harmful. Counselors should therefore not hesitate to discuss (potential) uncertain test results during *pretest* and *posttest* genetic counseling. It may, however, be beneficial to tailor the information on uncertain test results to the individual counselee based on personality characteristics, for example by discussing their informational needs and ability to deal with uncertainty [70,71].

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Declaration of Competing Interest

All authors declare to have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pec.2020.03.015.

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