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REVIEW

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Clinical outcomes of preimplantation genetic testing for hereditary cancer syndromes: A systematic review

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Abstract

Objective: To conduct a systematic review of the published literature on clinical outcomes following preimplantation genetic testing for monogenic disorders (PGT-M) for hereditary cancer syndromes (HCS).

Methods: Three electronic databases (PubMed, Cochrane, and EMBASE) were searched for publications related to PGT-M for HCS. When appropriate, weighted means were used to calculate clinical and live birth rates.

Results: We identified 22 publications that reported on clinical and/or psychosocial outcomes of PGT-M for HCS. The weighted mean clinical pregnancy rate (CPR) per embryo was 33.5% (11 studies, 95% CI: 29.1%, 38.2%), and the CPR per cycle with embryonic transfer was 40.1% (14 studies, 95% CI: 36.1%, 44.3%). The weighted mean live birth rate (LBR) per embryo was 28.9% (11 studies, 95% CI: 24.7%, 33.4%) and the LBR per cycle with embryonic transfer was 33.2% (13 studies, 95% CI: 29.2%, 37.4%). The limited literature regarding the psychosocial outcomes of PGT-M for HCS suggests reproductive decision-making is difficult and additional support may be desired.

Conclusion: These findings suggest that CPR and LBR following PGT-M for HCS are comparable to other monogenic disorders. Heterogeneity across studies suggests the overall CPR and LBR found may not be applicable to all HCS indications and PGT-M methodologies.

Key points

What is already known about this topic?

- Preimplantation genetic testing for monogenic conditions (PGT-M) is a reproductive option to reduce the chance of having a child with a heritable genetic condition.

What does this study add?

- This systematic review provides the most comprehensive synthesis of clinical outcomes of PGT-M for hereditary cancer syndromes (HCS).
- Overall, clinical pregnancy rates (CPR) and live birth rates (LBR) following PGT-M for HCS are similar to other monogenic disorders.

Findings were available as a virtual poster during the National Society of Genetic Counselors Annual Conference (Virtual conference, 2020).

1 | INTRODUCTION

Preimplantation genetic testing for monogenic disorders (PGT-M) with in vitro fertilization (IVF) offers an alternative approach to reproduction for prospective parents with heritable genetic conditions. The hallmark of this technology is embryo biopsy and subsequent genetic testing of amplified DNA–a process that has been successfully preventing the inheritance of monogenic disorders for over 30 years.[1] Research shows the live birth rate of PGT-M is similar to that of IVF.[2-5] Motivations for undergoing PGT-M include the desire for a healthy biologically related child, the avoidance of terminations or miscarriages, and a patient's perceived responsibility to their family and future child.[1,6,7]

Hereditary cancer syndromes (HCS) confer an increased lifetime risk of cancers or tumors. Individuals with HCS face similar reproductive decisions as others with heritable genetic conditions,[8] which may be impacted by genetic factors (e.g., mode of inheritance, age of onset, penetrance, severity), availability of screening and treatment (e.g., invasiveness, benefits, side effects), and the patient's own values and experiences.[6] Despite these similarities, hereditary cancer is unique in that those affected may require gonadotoxic treatments during their reproductive years, or they may wish to start their families at a younger age prior to undergoing risk-reducing surgery. In addition, some studies have noted that patients with certain HCS (e.g., BRCA1) may have reduced ovarian function compared to controls, which may impact outcomes of PGT-M.[9] The process of PGT-M as a reproductive option for prospective parents with HCS has been established, as the National Comprehensive Cancer Network (NCCN) recommends discussing this option in their guideline on genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer.[10]

To our knowledge, there has been no review of the efficacy of PGT-M for HCS and how it compares to other indications for PGT-M. Therefore, the objective of this study was to conduct a systematic review of published literature on clinical outcomes, specifically clinical pregnancy rate (CPR) and live birth rate (LBR), among individuals undergoing PGT-M for HCS. As a secondary objective, we aimed to report patient-reported psychosocial outcomes experienced during the process of PGT-M for HCS. Knowing more information about the clinical outcomes could help clinicians better counsel individuals with HCS about their reproductive choices, the likelihood of conception, and possibly to anticipate their psychosocial needs throughout the PGT-M process.

2 | METHODS

2.1 | Data sources and database search strategy

Three electronic databases (PubMed, Cochrane, and EMBASE) were searched on June 28, 2021 for English-language publications related to PGT-M for HCS. Search terms included PGT-M and its prior nomenclature (i.e., preimplantation genetic diagnosis [PGD]), combined with terms related to hereditary/familial cancers or tumors (e.g., hereditary neoplastic syndrome). In developing the search strategy and list of conditions for inclusion as hereditary cancer syndromes (HCS), we relied on a variety of published sources.[11,12] We also consulted with the authors of the ongoing National Society of Genetic Counselors Hereditary Cancer Genetic Counseling systematic review for their list of conditions and search strategy (Ravi Sharaf, MD and Julie Culver, MS personal communication, June 2019). Of note, although a few of the conditions are more commonly associated with benign tumors (e.g., Tuberous Sclerosis Complex, multiple exostoses), they do involve an increased cancer risk secondary to malignant transformation of those benign tumors. Search terms were limited to titles, abstracts, keywords, and appropriate medical subject (MeSH) headings. Reference lists of included publications were also evaluated for relevant articles. Please see Appendix A for additional search strategy details.

2.2 | Inclusion and exclusion criteria

Publications were included if they reported data on outcomes of interest for affected or pre-symptomatic individuals with a HCS. Hereditary cancer syndromes were defined as hereditary monogenic disorders in which increased susceptibility to cancer or tumors is one of the primary manifestations of disease (See Appendix A for additional information). Syndromes with increased cancer risk that are associated with severe manifestations of intellectual disability, hematological disease, or other symptoms were excluded (e.g., Sturge-Weber syndrome, Beckwith-Wiedemann syndrome, Sotos syndrome). Studies that evaluated the use of PGT-M HLA typing to produce unaffected stem-cell donor offspring for affected siblings (e.g., Fanconi anemia, Wiscott-Aldrich) also were excluded. Additional exclusions (e.g., animal or in vitro studies, PGT-M for other indications) are outlined in Figure 1. No exclusions were made based on publication date, study location, or study population demographics.

The first 70 abstracts were reviewed by all authors and discussed to ensure consistency among reviewers. The remaining abstracts were divided into thirds and reviewed by two-author pairs. If two or more authors determined that a publication likely contained the necessary outcome data, or provided relevant background knowledge, then the full-text article was obtained for further analysis. Each full-text publication was reviewed by at least two authors and the third author helped resolve discrepancies.

2.3 | Data abstraction and analysis

The first author (N.V.) abstracted relevant data into an evidence table (see Appendix B). All abstracted data was assessed for accuracy by a second author (E.C. or J.N.). Study characteristics (e.g., study years, location, population) were evaluated to assess for duplication of data

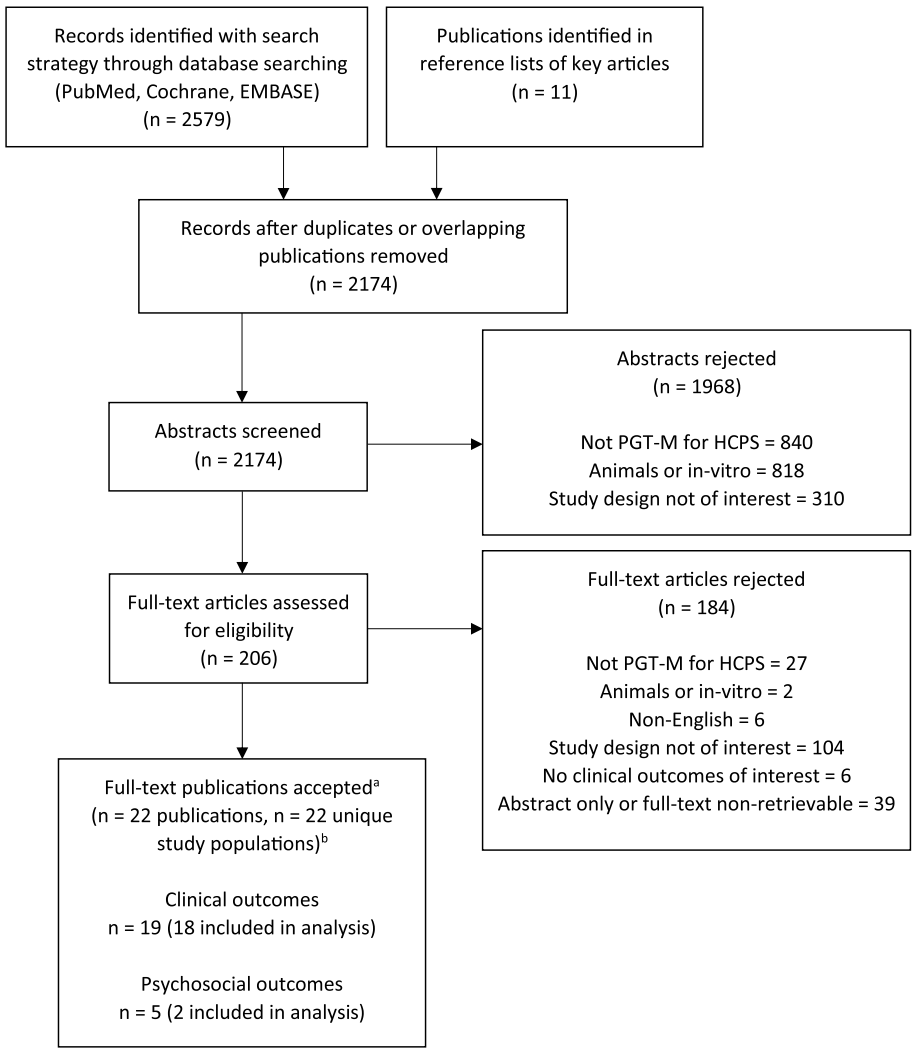

FIGURE 1 Systematic review PRISMA flow-chart. HCPS, hereditary cancer predisposition syndrome; PGT-M, preimplantation genetic testing for monogenic disorders

PGT-M, preimplantation genetic testing for monogenic disorders
HCPS, hereditary cancer predisposition syndrome

[a]Publications including either clinical or psychosocial outcomes were included; however, the categories were not mutually exclusive. Two publications included both.
[b]Two publications described the same study population, and one publication included two unique study populations.

across studies. If any publications had or were highly suspicious of study population overlap, only the study with the most comprehensive data was included.

Due to the heterogeneity of included publications with respect to design and outcomes, most findings were summarized using a narrative approach. When appropriate, weighted means were used to calculate the CPR and LBR. The rates were calculated using two different denominators: total embryos transferred, and total cycles with embryo transfer. Twin pregnancies were counted as two 'pregnancies' for the former and one 'pregnancy' for the latter. This distinction helped to differentiate between the likelihood of pregnancy/birth for each embryo transferred versus the likelihood of pregnancy/birth in a given cycle. Findings were presented for all publications overall as well as subgroups based on hereditary breast and ovarian cancer (HBOC) or other HCS.

This systematic review was registered with PROSPERO (CRD42021260697, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=260697). Since this review was focused on existing literature and did not directly evaluate data from human subjects, IRB or similar approval was not required.

3 | RESULTS

3.1 | Search strategy results and overview of studies

The search strategy identified 2579 publications, with eleven additional publications selected from reference lists of key-articles, for a total of 2590. After removing duplicates, 2174 abstracts were

TABLE 1 Overview of studies investigating the outcomes of preimplantation genetic testing for hereditary cancer syndromes

First author (Year)	Country	Study design	Study years	Clinical outcomes	Psychosocial outcomes	HCS		Total (*N*)[a]	Aneuploidy testing used	Female carriers *N* (%)	Male carriers *N* (%)
						HBOC	Other				
Rechitsky (2002)[13]	USA	Single-arm	NR	✓			✓	10	NR	6 (60)	4 (40)
Fiorentino (2003)[14]	Italy	Single-arm	NR	✓			✓	3	NR	NR	NR
Spits (2005)[15]	Belgium	Single-arm	NR	✓			✓	6	NR	NR	NR
Moutou (2007)[16]	France	Single-arm	2000–2005	✓			✓	4	NR	2 (50)	2 (50)
Spits (2007)[17]	Belgium	Single-arm	1998–2007	✓		✓	✓	10	NR	5 (50)	5 (50)
Sagi (2009)[18]	Israel	Single-arm	2006–2008	✓		✓		6	1 of 6	6 (100)	0
Vanneste (2009)[19]	Belgium	Single-arm	NR	✓			✓	3	2 of 3	3 (100)	0
Merker (2015)[20]	USA	Single-arm	2004–2013	✓			✓	77	10 of 77	51 (66)	26 (34)
Rubin (2014)[21]	USA	Single-arm[b]	2012	✓	✓	✓		6	NR	5 (83.3)	1 (16.7)
Derks-Smeets (2014)[22]	Netherlands & Belgium	Single-arm	2006–2011	✓		✓		71	71 of 71	42 (59.2)	29 (40.8)
Derks-Smeets (2014)[23]	Netherlands	Qualitative interviews and focus groups	2012		✓	✓		4	NR	NR	NR
Chow (2015)[24]	China	Single-arm	2007–2014	✓		✓	✓	NR[c]	0 of 8 cycles	NR	NR
Shapira (2015)[25]	Israel	Comparative	2003–2014	✓[d]		✓		62	NR	62 (100)	0
Goldman (2016)[26]	USA	Comparative[e]	2010–2014	✓		✓	✓	9	7 of 9	NR	NR
Dagan (2017)[27]	Israel	Qualitative interview	2013–2014	✓	✓	✓		18	NR	14 (77.8)	4 (22.2)
Derks-Smeets (2017)[9]	Netherlands & Belgium	Comparative	2006–2015	✓[f]		✓		43	43 of 43	43 (100)	0
Gietel-Habets (2018)[28,g]	Netherlands	Cross-sectional survey	NR		✓	✓		54	NR	NR	NR
		Focus group	2012					6	NR	4 (66.6)	2 (33.3)
Girardet (2018)[18]	France	Single-arm	2003–2015	✓			✓	56	0 of 56	NR	NR
Mor (2018)[29]	Israel & Canada	Survey/Questionnaire	2015		✓	✓		18	NR	18 (100)	0
Rechitsky (2018)[30]	USA	Single-arm	NR	✓		✓		79	51 of 79	NR	NR

TABLE 1 (Continued)

First author (Year)	Country	Study design	Study years	Clinical outcomes	Psychosocial outcomes	HCS		Total (N)[a]	Aneuploidy testing used	Female carriers N (%)	Male carriers N (%)
						HBOC	Other				
Yahalom (2018)[31]	Israel	Single-arm	2006–2015	✓			✓	4	NR	3 (75)	1 (25)
Wang (2020)[32]	China	Single-arm	2011–2018	✓			✓	3	3 of 3	2 (66.6)	1 (33.3)

Notes: Studies were sorted in chronological order by date of publication, and then in alphabetical order.

Abbreviations: HBOC, Hereditary Breast and Ovarian Cancer; HCS, Hereditary Cancer Syndrome; NR, Not reported or not reportable.

[a]Number of participants in publication who met the inclusion criteria; underwent preimplantation genetic testing for hereditary cancer or tumor susceptibility.

[b]Study is a subset of a larger qualitative, interview study.

[c]Number of participants not reported; however, 8 cycles were completed in participants who meet the inclusion criteria.

[d]Single-arm data, corresponding to participants meeting inclusion criteria, is included in quantitative outcome analysis.

[e]This study was compared *BRCA1/2* with other conditions. We included these comparative outcomes, and data from the *BRCA1/2* participants also were included in the primary analysis of clinical outcomes.

[f]The study compared *BRCA1/2* with other conditions. Although we included these comparative outcomes, we excluded it from the primary analysis of clinical outcomes since only first cycles were included and more comprehensive data are included in the study by Derks-Smeets (2014).[22]

[g]Publication has two separate study populations included (focus group vs. survey responders).

screened, and of those, 206 publications were selected for full-text review and 22 were accepted for inclusion (see Figure 1).

An overview of study characteristics is presented in Appendix C. Most studies were published between 2015 and 2020 in journals related to reproductive genetics or assisted reproduction. The accepted publications were sorted by indication for PGT-M (e.g., HBOC or other HCS) and categorized as having clinical outcomes, psychosocial outcomes, or both. Three studies included patients with HBOC as well as patients with other HCS, and these studies were grouped in the "other" category for all analyses.

An overview of the 22 included publications is presented in Table 1. A total of 18 publications were included in the analysis of clinical outcomes, and 5 studies reported psychosocial outcomes (studies not mutually exclusive). The 18 publications represent 433 total participants who underwent PGT-M for HCS, including six publications (n = 241) for HBOC and twelve publications (n = 192) for other HCS indications. Aside from HBOC, the most common conditions were neurofibromatosis (NF) type I (n = 90), familial adenomatous polyposis (n = 26), and retinoblastoma (n = 24). Please see Appendix D for additional information.

Of note, we identified 2 studies that compared PGT-M clinical outcomes for HBOC versus other conditions: Shapira et al. (2015) and Derks-Smeets et al. (2017). Findings from the HBOC arm of Shapira et al. (2015) are included in the analysis of clinical outcomes[25]; however, the HBOC arm of Derks-Smeets et al. (2017) overlaps with a more inclusive HBOC population reported in Derks-Smeets et al. (2014) and was therefore excluded from the weighted mean analysis of clinical outcomes.[9,22]

3.2 | Clinical pregnancy rate (CPR) and live birth rate (LBR)

Fourteen publications reported 536 total cycles with embryonic transfer, and ten publications reported a total of 412 embryos transferred. Sixteen publications reported a combined 222 pregnancies that were clinically confirmed via ultrasound which resulted in 211 liveborn children plus 5 awaiting delivery at the time of publication. Table 2 presents a summary of clinical outcomes: The weighted mean CPRs and LBRs per embryo transferred *and* per cycle with embryonic transfer. This data is reported across all HCS, for HBOC patients only, and for 'other HCS' only. Appendix E includes an expanded table with additional outcome data.

As noted previously, two comparative studies evaluated outcomes of PGT-M for HBOC carriers versus patients with other monogenic disorders. Derks-Smeets et al. (2017) compared 38 HBOC carriers and 154 controls who underwent PGT-M.[9] Although the number of mature oocytes was significantly lower in HBOC patients (particularly *BRCA1*) compared to controls, the CPR (per cycle with embryonic transfer) between the HBOC and control groups showed no significant difference with rates of 29.4% and 30.2%, respectively. The other comparative study by Shapira et al. (2015) compared 33 patients with HBOC to matched controls who underwent PGT-M.

TABLE 2 Quantitative analysis of PGT-M clinical outcome data for hereditary cancer syndromes

	Studies reporting	Patients[a]	Embryos transferred	Cycles with embryo transfer	Confirmed pregnancies or live births[b,c]	Associated rate (%)	95% confidence interval
Clinical pregnancy rate per cycles with embryo transfer					Pregnancies	CPR	
Overall	14	395		536	215	40.1	36.1, 44.3
HBOC only	5	223		261	125	47.9	41.9, 53.9
Other HCS	9	172		275	90	32.7	27.5, 38.5
Clinical pregnancy rate per embryo transferred					Pregnancies	CPR	
Overall	11	189	412		138	35.5	29.1, 38.2
HBOC only	2	85	158		80	50.6	42.9, 58.3
Other HCS	9	101	254		58	22.8	18.1, 28.4
Live birth rate per cycles with embryo transfer					Live births	LBR	
Overall	13	333		503	167	33.2	29.2, 37.4
HBOC only	4	161		228	97	42.5	36.3, 49.0
Other HCS	9	172		275	70	25.5	20.7, 30.9
Live birth rate per embryo transferred					Live births	LBR	
Overall	11	189	412		119	28.9	24.7, 33.4
HBOC only	2	85	158		71	44.9	37.4, 52.7
Other HCS	9	104	254		48	18.9	14.6, 24.2

[a]The number of patients noted here includes only those who met the inclusion criteria for this systematic review (i.e., patients with HCS who attempted PGT-M).

[b]Twin pregnancies were counted as two pregnancies for calculations involving number of embryos transferred, and as a single pregnancy when calculating rates per transfer. Live births involving more than one child included all children born when calculating rate per number of embryos transferred but were classified as a single live birth when calculating the rate per transfer.

[c]Ongoing pregnancies at the time of publication were not included in analysis.

The CPR per cycles completed with embryonic transfer were 33.3% for the HBOC participants and 22.2% for the matched controls, which showed no significant difference ($p = 0.44$). Unlike the previous publication, this study determined that both healthy and HBOC carriers (who were affected with cancer) demonstrated normal ovarian response in IVF cycles.[25]

3.3 | Preimplantation genetic testing for aneuploidy (PGT-A)

Ten publications discussed aneuploidy testing of embryos (see Table 1). Two studies specifically noted that PGT-A was not used in any cases due to legal restrictions[15] or a lack of indication.[24] Of the studies that did use aneuploidy testing, the methodology was highly variable. Two studies (three publications) focused exclusively on aneuploidy of the single chromosome that was also being testing for PGT-M,[9,19,22] and one study noted that a single patient had limited aneuploidy testing for chromosomes 21, X, and Y.[18] The remaining four studies used more rigorous approaches, including next-generation 24-chromosome aneuploidy screening[20,26,32] or a variety of approaches based on the best technology available at the time (e.g., FISH, PCR, array-CGH, 24-chromosome aneuploidy screening).[30] However, the application of aneuploidy testing in these four studies was not universal, with a weighted mean use of 42% (71 of 168 patients, range: 13%–100%). The remaining publications did not mention if PGT-A was used or not. Unfortunately, the limited reporting on PGT-A and variable uptake precluded subgroup analyses of clinical outcomes based on the use of PGT-M with PGT-A versus PGT-M alone.

3.4 | Prenatal and postnatal confirmation of PGT-M

Ten publications reported on the use of invasive prenatal diagnosis (PND) to confirm an unaffected pregnancy. The majority (6 of 10, 60%) did not use PND.[16-19,21,27] The publications that reported using confirmatory testing differed in their approach. Derks-Smeets et al. (2014) noted that PND was performed for only four of the 45 pregnancies (all of which confirmed an unaffected pregnancy), while Chow et al. (2015) reported that either prenatal or postnatal diagnosis was utilized for every pregnancy.[22,24] Two of the three patients in Wang et al. (2020) underwent PND.[32] Girardet et al. (2018) noted that 21/24 pregnancies in their total cohort underwent PND; however, it is unknown which of these patients had PND for HCS.[33]

Given the lack of reporting with respect to confirmatory diagnostic testing, we were unable to perform a quantitative

TABLE 3 Summary of psychosocial outcomes of PGT-M for hereditary breast and ovarian cancer syndrome

Outcome/Measure/Predictor	Summary of process and outcome findings[a]
Regret (DRS scale; Mean [SD])	• Discussed in two publications • Mor et al. (2018) found participants who did not undergo PGT-M for HBOC had higher decisional regret (26.6 [21.0]) than participants who did (20.0 [20.6]); however, this difference did not reach significance ($p = 0.25$) • Derks-Smeets et al. (2014) found that none of the couples who underwent PGT-M regretted their choice, but they did not anticipate the associated psychological strains
Satisfaction (SWD scale; Mean [SD])	• Discussed in two publications • Mor et al. (2018) found satisfaction was significantly higher among participants who opted to undergo IVF with PGT-M (4.4 [0.7]) compared to those who did not (3.9 [1.0]) ($p < 0.04$) • Gietel-Habets et al. (2018) focus group couples were generally positive about their decision to receive reproductive counseling that discussed the clinical and practical aspects of PGT-M, even if they opted to not undergo PGT-M
Perceived difficulty of reproductive decision-making (Revised illness perception questionnaire)	• Discussed in one publication but two unique studies • Survey responses analyzed by Gietel-Habets et al. (2018) identified three predictors of perceived decision-making difficulty ○ *Younger participants* ($P = 0.042$, $\beta = -0.047$, 95% CI, −0.091 to −0.002) ○ *Participants who ultimately opted for natural pregnancy* ($P = 0.025$, $\beta = -0.560$, 95% CI, −1.048 to −0.073) ○ *Participants with a previous mastectomy* ($P = 0.059$, $\beta = 0.263$, 95% CI, −0.023 to 1.134)[b] ○ All 18 couples who participated in the focus group performed by Gietel-Habets et al. (2018) reported PGT-M decision-making as difficult
Need for psychological support	• Discussed in two publications but three unique studies • Survey responses analyzed by Gietel-Habets et al. (2018) identified two groups of participants who had a significantly increased need for psychological support ○ *Partners of carriers* ($p = 0.038$, odds ratio = 0.168, 95% CI, 0.031–0.907) ○ *Religious Participants* ($p = 0.089$, odds ratio = 4.171, 95% CI, 0.805–21.614) • The majority (61%) of survey responders believed psychological support should be routinely offered and 17% believed a consultation with a social worker or psychologist should be mandatory • All participants in the focus groups performed by Gietel-Habets et al. (2018) and Derks-Smeets et al. (2014) expressed a need for psychological support during decision-making
Need for support tools	• Discussed in one publication but two unique studies • Most survey responders (69%) in Gietel-Habets et al. (2018) and focus group couples indicated that any support tool (contact with other couples, decision aid, consults) would've improved decision-making • Two groups of survey responders had a stronger need for decision-support tools ○ *Those who perceived HBOC as more serious* ($P = 0.074$, $\beta = 0.341$, 95% CI, −0.034 to 0.715) ○ *Those who ultimately opted for PGT-M or prenatal diagnosis* ($P = 0.096$, $\beta = 0.511$, 95% CI, −0.093 to 1.116)
Predictors for undergoing PGT-M	• Discussed in three publications by Derks-Smeets et al. (2014), Dagan et al. (2017) and Mor et al. (2018) • The only statistically significant predictor associated with the decision to undergo PGT-M was previous infertility ($p < 0.001$) • Other predictors that were evaluated and either were common and either not assessed for or did not meet significance: ○ Having witnessed the disease in a close relative ○ Having pre-existing frozen embryos ○ Good accessibility and reimbursement options

(Continues)

TABLE 3 (Continued)

Outcome/Measure/Predictor	Summary of process and outcome findings[a]
Predictors for not undergoing PGT-M	• Discussed in two publications by Derks-Smeets et al. (2014) and Dagan et al. (2017) • Common predictors[c]: ○ Cancer risk associated with ovarian stimulation ○ Low chance of successful pregnancy ○ Loss of romance and control regarding pregnancy ○ Logistical and financial burden ○ Psychological stress

Abbreviations: CI, Confidence Interval; DRS, Decisional Regret Scale; HBOC, Hereditary Breast and Ovarian Cancer; PGT-M, Preimplantation Genetic Testing for Monogenic Disorders; SD, Standard Deviation; SWD, Satisfaction with Decision Scale.

[a]Includes data from 5 publications representing 6 unique study populations.

[b]Trending towards significance.

[c]Were not evaluated for significance.

analysis of the false-negative rates of PGT-M. Nine of 15 publications directly or indirectly reported no false-negatives in their study,[13,15,17,19,22,24,30,31,33] but only four described how that testing was performed (i.e., postnatally[17,19] or prenatally).[22,33] One publication performed post-PGT-M reanalysis of all embryos, which showed concordant results.[17]

3.5 | Psychosocial outcomes

Five publications representing six unique study populations addressed psychosocial outcomes of PGT-M.[21,23,27-29] All of these studies focused on HBOC. The main findings of four of these publications are outlined in Table 3. The fifth publication, a collection of narrative case reports by Rubin et al. (2014), represented the personal experiences of ten BRCA carriers' attitudes toward and experiences with PGT-M.[21] Although limited, evidence from these studies suggested that reproductive decision-making in this context is difficult and additional psychological support may be desired.[23,28]

4 | DISCUSSION

To our knowledge, this systematic review provides the most comprehensive synthesis of clinical outcomes of PGT-M for HCS to date. Previous research has shown that the process of PGT-M does not hinder the efficacy of IVF.[4] Based on previous literature, the CPRs when PGT-M is performed for any monogenic indication typically range between 20% and 40%.[2,3,14,33,34] For the PGT-M studies on HCS reported in this systematic review, the estimated CPR was 33.5% and 40.1% and LBR was 28.9% and 33.2% (per embryo and per cycle with transfer, respectively). These results indicate reasonable success rates when PGT-M is performed for HCS and may be similar to those reported for other PGT-M indications.

When reviewing the CPR and LBR for HBOC independently, the weighted mean CPR (50.6% per embryo and 47.9% per cycle with embryo transfer) and LBR (44.9% per embryo and 42.5% per cycle with embryo transfer) for HBOC are higher than what has been generally been reported for all monogenic disorders.[2,3,14,33,34] In our review, there was sufficient literature regarding the use of PGT-M for HBOC to review. Although only six of the 18 publications included in the analysis were focused on HBOC, there were 241 participants; more than half of the total number identified. The publications related to HBOC also were more recent (five-sixths published in the last six years) and may have benefited from newer amplification technology, concurrent aneuploidy assessment, and practice guidelines for methodology, resulting in higher CPR and LBR than previous 'proof of concept' studies.

Data regarding the gene involved (*BRCA*1/*BRCA*2) were extracted when possible; however, outcome data for HBOC studies didn't always report on these parameters separately, making comparison difficult. Although *BRCA*1 and *BRCA*2 both cause HBOC, there is conflicting evidence in the literature suggesting reduced fertility (e.g., ovarian reserve, pregnancy rates, birth rates) among carriers and possibly discordance between women with *BRCA*1 and *BRCA*2 pathogenic variants.[9,25,35-38] Our review cannot elucidate differences between *BRCA*1 and *BRCA*2 with respect to CPR and LBR, but it suggests the reproductive outcomes for HBOC carriers may be similar to what has been reported in the literature.

For patients with a history of cancer, both their risk of infertility and potential outcomes of future IVF are difficult to predict, as these outcomes vary between patients and are affected by treatment factors. Regardless, rates of pregnancy following IVF among cancer survivors are generally lower than age-matched peers.[39] A study by Ginsburg et al. (2001) showed that women who underwent chemotherapy for early breast cancer had fewer retrieved oocytes and embryos during IVF than women undergoing retrieval prior to chemotherapy.[40] Among the publications in this review, HBOC studies often excluded women who had previous cancer treatment or those with diminished ovarian reserve, but few studies for other HCS mentioned whether participants were unaffected carriers or previously affected. We were not able to assess any potential differences in CPR or LBR between pre-symptomatic carriers and previously affected participants, for any indication. A study included in our quantitative analysis by Derks-Smeets et al. (2014) did comment on the efficacy of PGT-M for both pre-symptomatic carriers and BRCA-

positive female breast cancer survivors, which showed comparable CPRs.[22]

Although the 'other' HCS made up the majority of publications in this review, the number of overall participants was only about half of patients included–encompassing twelve different HCS (including HBOC in three studies[17,24,26]). Given the body of research supporting the efficacy of PGT-M among all indications,[3,41] the CPR and LBR for HCS other than HBOC seem lower than anticipated (e.g., CPR per cycle was 32.7% for 'other' HCS vs. 47.9% for HBOC; CPR per embryo was 22.8% for 'other' HCS vs. 50.6% for HBOC). A potential explanation is the small sample size of these studies (ten of the twelve studies had ten or fewer participants), and the 'proof of concept' methodology of these earlier publications–often providing the first PGT-M experience for an indication or the first clinical application of a proposed analysis method. Even with CPR and LBR being lower than expected for this group, there were live births reported in ten of the twelve publications, and for 11 of the 12 indications included (Zero live births recorded for Peutz-Jeghers).

The process of PGT-M accompanied by PGT-A has been referred to as 'combined PGT'.[15] In our review, 10 studies made any mention of aneuploidy testing, although only 4 studies used rigorous approaches to PGT-A, such as next-generation 24-chromosome aneuploidy screening.[20,26,30,32] In addition, the use of PGT-A within these studies was not universally applied to all patients. Although PGT-A has been reported to increase LBR during IVF,[42] we did not have enough information to determine the impact of PGT-A in our review given the limited number of studies that clearly documented its use and the variable application within studies. Lastly, we could not assume that a failure to mention PGT-A meant that it was not used. Although this may be the case for older studies, more recent studies may be less likely to mention PGT-A since aneuploidy assessment is a standard companion test for PGT-M at some institutions.[43] Future studies on PGT-M should clearly report whether PGT-A was used, what method was employed, how many patients/embryos had combined PGT-M with PGT-A versus PGT-M alone, and any impact of PGT-A on pregnancy outcomes.

Confirmatory prenatal diagnosis (PND) is a recommended component of PGT-M and can provide evidence of false-negatives or misdiagnoses.[44,45] A misdiagnosis may be technical (contamination of sample, failed amplification of DNA), biological (mosaicism, undetected crossover events), or human (sample mix-up) in error.[46] In our review, only nine of the 18 studies included in the quantitative analysis discussed false-negatives, but only four provided additional explanation regarding the way it was assessed (prenatal[22,33] vs. postnatal[17,19] testing). Most publications that commented on the use PND, did not use it. This limited use of PND is in stark contrast to current recommendations. Literature is currently lacking on the overall uptake of PND for PGT-M patients in general; therefore, we cannot comment on whether this finding is unique to HCS patients. Given the adult-onset nature and the unique fertility concerns for patients with HBOC, participants in the study by Derks-Smeets et al. (2014) were comfortable accepting a "reduced risk" of having a child with HBOC and were less likely to terminate an affected pregnancy–especially if conception was prior to treatment or prophylactic surgery, if there was limited fertility, or there were a finite number of frozen embryos. In the study by Sagi et al. (2009), describing their clinic's experience with PGT-M for HBOC, authors went so far as to say that "confirmatory prenatal diagnosis may not always be encouraged."

Data regarding the psychosocial outcomes of PGT-M for carriers of HCS was lacking. Much of the current literature surrounds prospective patients' attitudes toward the option of PGT-M; however, a conceptual framework derived from psychological theory, for navigating decisional-distress during PGT-M, was proposed by Pastore et al. (2019). It suggests that there are three categories of contributing factors to decisional distress during PGT-M: intraindividual, interpersonal, and situational factors.[47] To our knowledge, this framework has yet to be applied to the HCS population. For the psychosocial data that was available for review, it only applied to carriers of HBOC. Even with limited data, evidence suggests that carriers of HBOC also experience significant decisional stress and need psychological support throughout the process of IVF and PGT-M. Survey respondents in Gietel-Habets et al. (2018) indicated the need for support tools, specifically the ability to learn more about other couples' experiences through the process. The narrative interview by Rubin et al. (2014), also included in this review, represents an example of a potential support resource, which describes other patients' unique motivations, fears, and either regret or satisfaction with their experience.

5 | LIMITATIONS

This systematic review has some limitations. For HBOC studies, only two studies reported enough information to calculate CPR and LBR on a per-embryo basis[18,30]; therefore, our calculations may not be an accurate representation of the true CPR and LBR among patients with HBOC. For studies on HCS other than HBOC, the number of participants was limited; aside from Merker et al. (2015), which included 77 patients with NF1, each study included 16 participants or fewer for each indication. For studies representing multiple HCS, the outcome data were abstracted together. For Chow et al. (2015), only number of cycles per indication was known, not number of participants–so we used that data in its place for the quantitative analysis. For Merker et al. (2015) we used the midpoint between the 'observed' and 'estimated' outcome data for our calculations of CPR. We did not account for differences in the type of genetic testing methodology being utilized for PGT-M, IVF-related technical issues or provider technical expertise, parental age differences, individual clinic success rates overall, or other factors that may influence overall CPR or LBR. Therefore, overall CPR and LBR for HCS in our study may not be generalizable to a broader patient population seeking PGT-M for HCS. Additionally, many relevant publications regarding research on PGT-M for HCS were unfit for inclusion as outcome data for HCS were not reported independently of other monogenic non-cancer indications.

6 | FUTURE RESEARCH

The lack of research exploring the psychosocial outcomes of the process of PGT-M for HCS patients represents a significant gap in the literature. Additional studies that evaluate psychosocial outcome will help improve management, influence anticipatory guidance, and promote the use of support tools and patient referrals for psychological support. In addition, there were few data available on the clinical outcomes of PGT-M for HCS other than HBOC, but all HCS were lacking important clinical outcome data for analysis. Since it is likely this data was captured in some form but not reported, future research should aim for more complete and comprehensive reporting of PGT-M outcomes. Lastly, our review captured several study characteristics that were not analyzed in detail. These characteristics may or may not influence reproductive outcomes (e.g., sex of carrier, method of PGT-M used, previous cancer history, and use of fresh vs. frozen embryos). Further exploration into the effect of any of these variables on CPR and LBR may provide useful information.

7 | CONCLUSION

This systematic review provides data on reproductive outcomes (e.g., CPR and LBR) of PGT-M. Evidence from this review suggests that the overall CPR and LBR per embryo and per transfer for HCS may be similar to that of other monogenic disorders for which PGT-M is used. We were not able to determine whether or not PGT-A impacts birth outcomes for PGT-M, and we suggest that future research on PGT-M should clearly report this methodological detail. Although the evidence on psychosocial outcomes is limited and focused exclusively on HBOC, these preliminary findings suggest that decisions on whether to undergo PGT-M may cause stress and patients desire additional psychosocial support throughout the process. Hopefully, this information can be used to better counsel individuals with HCS about their reproductive choices, the likelihood of conception, and to anticipate their psychosocial needs during decision-making and afterward.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing of evidence table and base calculations are available upon request.

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