SYSTEMATIC REVIEW | Genetics inMedicine

High-risk consumers' perceptions of preimplantation genetic diagnosis for hereditary cancers: a systematic review and meta-analysis

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Individuals carrying deleterious germline mutations placing them at increased risk for hereditary cancer syndromes (high-risk consumers) often have a great deal of fear and concern over transmitting mutations to their offspring, particularly conditions which are autosomal dominant. Preimplantation genetic diagnosis (PGD) is a procedure that can detect certain germline cancer predisposing mutations present in embryos. The objective of this review was to assess high-risk consumers' knowledge and perceptions of PGD for hereditary cancers. A systematic literature review was conducted through PubMed, Wiley Interscience, PsychInfo, and Cochrane Library databases to identify all articles assessing consumer knowledge and attitudes of PGD for hereditary cancer syndromes. We assessed heterogeneity and the robustness of findings through additional analyses according to study location, hereditary cancer type, and sample size. Thirteen articles remained eligible after the application of specific criteria. Results show a general low level of knowledge about PGD for hereditary cancers, moderate rates of acceptability among high-risk groups, and high levels of need for information about PGD. Individuals in specific risk groups such as those with a personal or family history of hereditary breast and ovarian cancer (HBOC) syndrome or familial adenomatous polyposis (FAP) may benefit from educational information from healthcare professionals about the use of PGD.

Genet Med 2012:14(2):191–200

Keywords: hereditary cancers; perspectives; PGD; psychology; psychosocial

INTRODUCTION

Emerging technology has enhanced the practice of risk management of hereditary cancer syndromes. Approximately 5–10% of all cancers are caused by inherited mutations in cancer predisposing genes.[1–3] Preimplantation genetic diagnosis (PGD) is a procedure used to test embryos for genetic disorders before uterine implantation.[4–7] PGD has been used to avoid both the potential risks of miscarriage associated with amniocentesis and chorionic villus sampling and decisions about pregnancy termination if the fetus is found to be affected following prenatal diagnosis. PGD may be performed by a variety of methods including biopsy on embryos at the eight-cell stage after a 3-day culture or blastocyst stage after 5- to 6-day culture, with a small sample removed for DNA testing for a specific gene mutation.[8] Using the information obtained from DNA testing for germline mutations in the parents, couples may consent to implanting embryos in accordance with physician recommendations or national policies.

Individuals who carry mutations in hereditary cancer predisposition genes can have psychological concerns and stress regarding the implications of their genetic status. The possibility of transmitting a mutation to a child may pose a concern to families to the extent that some carriers may avoid childbearing.[9–11] For the purposes of this review, we refer to individuals at risk for hereditary cancers as high-risk consumers.

There are medical and ethical concerns related to PGD. PGD requires the *in vitro* fertilization (IVF) process, which puts children at a higher risk for the genomic imprinting disorders Beckwith-Wiedemann syndrome,[12] Angelman syndrome, and Prader-Willi syndrome.[13] Because PGD is procedurally performed in conjunction with standard IVF procedures, it is difficult to know whether these adverse outcomes are the result of PGD or the IVF process, although recent research suggests that there are no significant differences found between the outcomes of PGD born children and IVF born children.[14–16] Ethical concerns of IVF and PGD include the potential discarding of embryos that are positive for the hereditary condition, the long-term storage of embryos, and embryo donation.[17–19]

A considerable amount of research has focused on the ethical implications of PGD for gender selection and other physical attributes, a relatively new use of PGD. Less is known about knowledge, attitudes, and perceptions about PGD use among individuals at risk for adult onset conditions, in particular cancer (high-risk populations). The limited available studies that do report on high-risk consumers' knowledge of PGD

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Submitted 3 May 2011; accepted 14 July 2011; advance online publication 13 September 2011. doi:10.1038/GIM.0b013e31822ddc7e

for hereditary cancer show high variability across results. For example, Vadaparampil et al.[20] found that 33% of those at risk for transmitting hereditary breast and ovarian cancer (HBOC) would consider PGD, whereas Staton et al.[21] found that only 13% of HBOC carriers would consider PGD. As genetic testing for hereditary cancer susceptibility continues to become integrated into clinical practice, there will likely be more individuals seeking information about PGD as part of their reproductive decision-making.[22,23] Although PGD has not been legalized in all countries, informed decision-making about PGD and other health- and ethics-related concepts should be based on totality of the existing evidence and baseline levels of perceptions toward PGD. Accordingly, we have performed a systematic review and meta-analysis on PGD and high-risk consumers specifically for cancer. The objective was to perform a synthesis of all relevant studies on the subject to provide an accurate assessment on what is currently known about high-risk consumers' perceptions of PGD.

METHODS

Literature search

An electronic search was performed in the databases of PubMed, Cochrane Library, Wiley Interscience, and PsychInfo. The search was limited to prospective studies including cross-sectional, cohort, and case-control from January 1992 to December 2009. Because PGD was not available for the diagnosis of hereditary cancers until 1992, the search included articles published after this year. The search was limited to English language publications because primary use of PGD is in high resource countries. Moreover, PGD has been used in some animal studies, therefore using this limitation assured we only retrieved studies on humans.

Search terms included the following: "patient education" and "preimplantation genetic diagnosis" or "preimplantation genetic diagnosis" and "health literacy" and "knowledge" and "cancer" or "neoplasms [Mesh]" or "opinion" and "choice" and "attitudes" and "PGD" and "decision-making" or "demand" and "consumers" and "hereditary cancer" and "reproduction" or "managing cancer" and "BRCA" or "BRCA1" and "ovarian cancer" and "attitudes of high-risk" or "inherited cancer predisposition."

Inclusion and exclusion criteria

Any prospective study that assessed perspectives of PGD in individuals at high-risk for hereditary cancer and enrolled a minimum of 10 subjects was eligible for inclusion in this systematic review. Qualitative and quantitative studies were eligible for inclusion. Studies were excluded if they (1) addressed PGD for noncancer-related genetic conditions; (2) focused only on procedures within assisted reproductive technology in general without use of PGD; (3) focused on the healthcare provider perspective; and (4) assessed perspectives of PGD retrospectively.

Study selection and data extraction

Two reviewers (D.M. and A.K.) independently appraised the list of references and assessed the studies for eligibility. Any disagreements were resolved by discussion until consensus was reached. Data were extracted on the study design; study population characteristics such as cancer type, sex, age, and religion; study time frame, assessment method, and knowledge; personal acceptability; social acceptability; and perceived advantages and disadvantages of using PGD for hereditary cancer. We also extracted data on the methodological quality of the included studies.

Statistical analysis

Descriptive methods were used in the case of qualitative studies and not included in the subsequent analyses. In the case of quantitative studies, for the purpose of meta-analysis, we first transformed the proportions of extracted data into a quantity according to the Freeman-Turkey variant of the arcsine square root transformed proportion.[24] The pooled proportion was calculated as a back-transformation of the weighted mean of the transformed proportions, using the random effects model. A formal statistical test for heterogeneity using the I^2 test[25] was performed. We also explored heterogeneity and the robustness of the findings by conducting sensitivity analyses for the outcomes of personal acceptability of PGD among high-risk consumers, in addition to acceptability of PGD for others at high risk for hereditary cancer, assessed in relation to study characteristics of location, sample size, and type of hereditary cancer. The possibility of publication bias was also assessed using the Begg and Egger funnel plot method.[26,27] Despite its limitations, this method is widely used to assess publication bias.[28] We evaluated the methodological quality of individual studies using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.[29] Individual studies were evaluated to assess whether each item on the STROBE checklist was met or not met. The meta-analysis was performed using Stats Direct software. The work was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.[30]

RESULTS

Identification of studies

The Appendix (**Supplementary Data** online), outlines the process of identification and selection of studies. The initial search yielded 195 studies at the outset; 41 were excluded once identified as duplicates. Of the remaining 154 studies, 34 additional articles were excluded for reasons shown in the Appendix (**Supplementary Data** online). Abstracts of the remaining 120 were reviewed removing an additional 107 articles largely due to the lack of focus on PGD use for hereditary cancer. The final review extracted data on 13 studies that met the inclusion criteria.

Characteristics of studies

Characteristics of the included studies are summarized in **Table 1**. Of the 13 included studies, 54% (7/13) assessed consumer attitudes toward PGD for HBOC,[11,20,21,31–34] 15% (2/13) Familial

Table 1 Characteristics of studies and participants

Author	Mean age (range)	Study design	Female participants, *n/N* (%)	Consider themselves religious, *n/N* (%)	PGD legal for hereditary cancer at time of study
US-based studies					
Kastrinos et al.[36]	42 (28–73)	Cross-sectional survey	13/20 (65)	14/20 (70)	✓
Quinn et al.[34]	NR (22–38)	Cross-sectional survey	111/111 (100)	104/111 (94)	✓
Quinn et al.[32a]	NR	Qualitative	446/446 (100)	365/446 (82)	✓
Staton et al.[21]	34 (25–40)	Cross-sectional survey	213/213 (100)	NR	✓
Vadaparampil et al.[20]	NR	Cross-sectional survey and qualitative	962/962 (100)	(>_50)	✓
Non–US-based studies					
Borkenhagen et al.[38]	35 (22–56)	Cross-sectional survey	265/530 (50)	242/265 (91)	
Douma et al.[35]	44 (16–84)	Cross-sectional survey	242/525 (46)	NR	
Fortuny et al.[11]	42 (19–88)	Cross-sectional survey	67/77 (87)	32/77 (42)	✓
Krones et al.[39]	— (20–50)	Cross-sectional survey	162/324 (50)	NR	✓
Lammens et al.[37]	40 (16–75)	Cross-sectional survey	88/179 (49)	122/179 (68)	✓
Meister et al.[40]	36 (18–50)	Cross-sectional survey	1,181/2,110 (56)	1,576/2,110 (75)	
Menon et al.[31]	43 (median) (30–69)	Cross-sectional survey	52/52 (100)	23/52 (44)	✓
Sagi et al.[33]	34 (29–38)	Case report	10/10 (100)	NR	✓

NR, not reported; PGD, preimplantation genetic diagnosis.
[a]Not included in meta-analyses. Duplicate values with the study by Vadaparampil et al.[20]

adenomatous polyposis (FAP),[35,36] 8% (1/13) Von Hippel-Lindau and Li-Fraumeni syndrome,[37] and 23% (3/13) attitudes of PGD for hereditary cancers in general.[38–40]

Total enrollment from all 13 studies was 5,294 participants, with a pooled average response rate of 75%. Twenty-three percent (3/13) of studies[20,39,40] did not report the response rate of high-risk consumers, while the response rate in the qualitative study by Quinn et al.[32] was not counted because this study used a subset of participants from the study by Vadaparampil et al.[20] All studies were prospective, cross-sectional with 10 using strictly quantitative methods,[11,21,31,34–40] 1 qualitative methods,[32] and 2 mixed methods.[20,33] The median sample size was approximately 213 participants (range, 10–2,110). Thirty-one percent (4/13) of studies[20,31,33,34] only recruited female participants, while the remaining studies recruited male and female participants. Twenty-three percent (3/13) of studies[35,37,38] included partners or family members. The age of the participants ranged from 16 to 75 years in all included studies. Only one study reported the median age of participants,[43,31] while 69% (9/13)[11,21,33,34,36–40] reported average age, making the overall average age of high-risk participants 37.8. Three studies did not indicate either median or average age of participants.[20,32,39] Krones et al.[39] only reported age of female participants as <40 years and male participants as <50 years. Fifty-four percent (7/13) of studies[11,31,32,36–38,40] assessed religion among the participants. Only 23% (3/13) of studies[32,36,38] reported race/ethnicity of participants. All studies reported that at least 50% of the participants already had children. All studies recruited participants from existing clinic and hospital databases. Eighty-five percent (11/13) of the included studies[11,20,21,31,34–40] described using statistical methods for data analysis such as Fisher's exact, χ^2, and x^2 tests. Staton et al.[21] used participant scores from the State-Trait Anxiety Inventory for Adults and the Impact of Event Scale Scores for the calculation of counts, proportions, and means through descriptive analyses. The study by Quinn et al.[32] is a qualitative study that used hand-coding and constant comparative method of themes presented. Sagi et al.[33] did not discuss any data analysis methods in their mixed-methods study.

Methodological quality

The methodological quality as assessed by the STROBE guidelines varied across studies. Only 39% (5/13) of studies[11,31,34,35,37] indicated the number of participants with missing data for each variable tested.

Regarding outcomes, 100% of studies indicated unadjusted estimates of results for each variable of interest; however, only 23% (3/10) of studies[21,35,37] reported category boundaries when continuous variables were categorized. Twenty-three percent (3/10) of studies[37–39] did not report limitations or bias of each study. Moreover, 54% (7/13) of studies[20,21,31,32,34–36] discussed the external validity specifically in that results may be limited to heterogeneous populations. Sixty-two percent (8/13) of studies[11,20,32,35,37–39,40] reported their source of funding.

Publication bias

Publication bias in the included studies was evaluated using the Begg and Egger funnel plot for the following outcomes: knowledge, personal use, offered to others, avoiding termination of pregnancy, ethical implications, and cost.[26,27] This showed no asymmetry indicating the absence of publication bias. However,

for the outcome concern for future offspring, there was an asymmetrical distribution indicating the possibility of a publication bias (*P* value = 0.0101).

OUTCOMES

Results including knowledge, attitudes, and acceptability are summarized in **Figures 1–3**. Only data from quantitative studies were used for the purpose of synthesis.

Knowledge of and attitudes toward PGD for hereditary cancer

Data on overall knowledge of PGD for the use of hereditary cancer were extractable in 54% (7/13) of studies.[20,33–35,38–40] Altogether, these seven studies enrolled a total of 4,642 subjects. The pooled response rate was 35% (95% CI [confidence interval], 30–50%) indicating that a majority of respondents, on average, had no knowledge of PGD. However, there was a

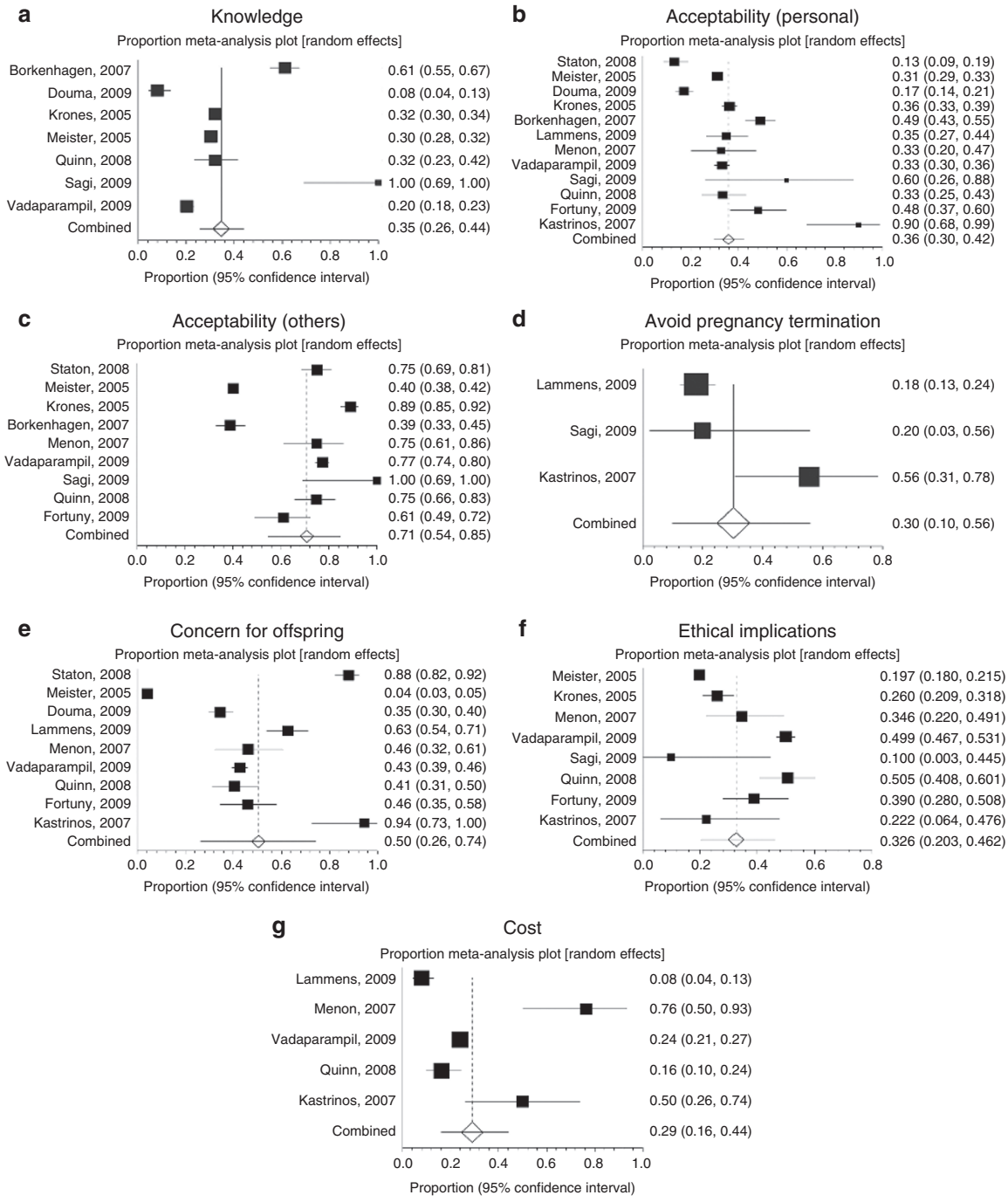

Figure 1 Overall outcomes of high-risk consumers' concerns and perceptions of preimplantation genetic diagnosis.

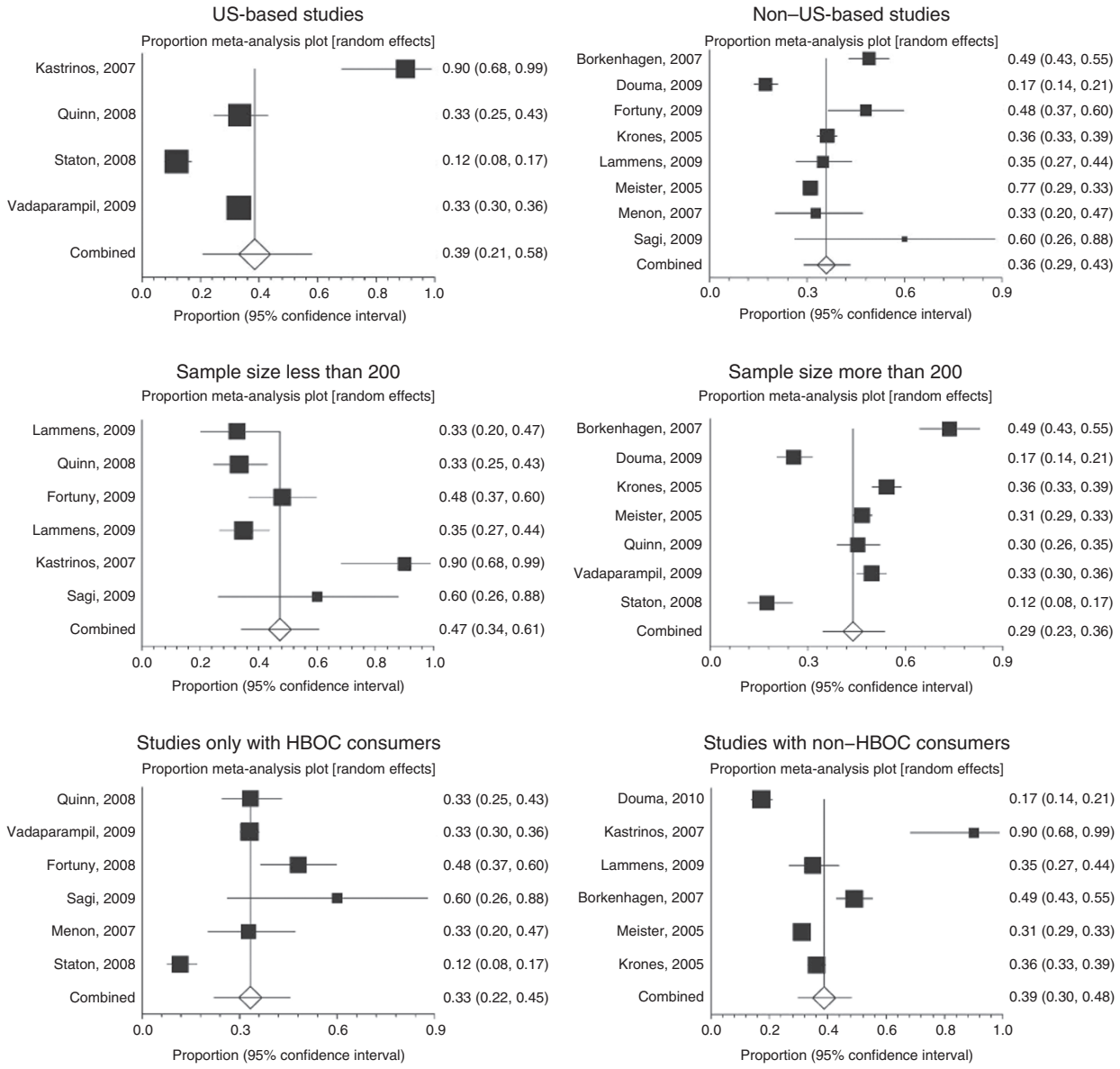

Figure 2 Sensitivity analyses: personal acceptability of high-risk consumers. HBOC, hereditary breast and ovarian cancer.

statistically significant heterogeneity in the included studies for the outcome of knowledge of PGD (I^2 = 97.9%; P < 0.0001).

Acceptability of PGD for hereditary cancer

Personal use. Data on participants' willingness to use PGD themselves for hereditary cancer were extractable in 100% (13/13) of studies. The pooled response was 36% (95% CI, 30–42%) indicating that the majority of respondents, on average, would not use PGD themselves. There was a statistically significant heterogeneity in the included studies for the outcome of personal use of PGD (I^2 = 93.9%; P < 0.0001). In the qualitative study by Quinn et al.,[32] 30% (135/446) noted favorable attitudes for personal use.

Should PGD be offered to other high-risk consumers. Data on respondents indicating that PGD should be offered to other consumers at high-risk for hereditary cancers were extractable in 69% (9/13) of studies.[11,20,21,31,33,34,38–40] The pooled response was 71% (95% CI, 54–85%) indicating that the majority of respondents, on average, believe that PGD should be offered to other high-risk consumers. There was a statistically significant heterogeneity in the included studies for the outcome of knowledge of PGD (I^2 = 98.9%; P < 0.0001). In the qualitative study by Quinn et al.,[32] 32% (142/446) noted favorable attitudes for use of PGD by other high-risk consumers.

Use of PGD to avoid a pregnancy termination. Data on respondents indicating that PGD is an acceptable option in order to avoid a pregnancy termination were extractable in 23% (3/13) of studies.[33,36,37] The pooled response was 30% (95% CI, 10–56%) indicating that the majority of respondents, on

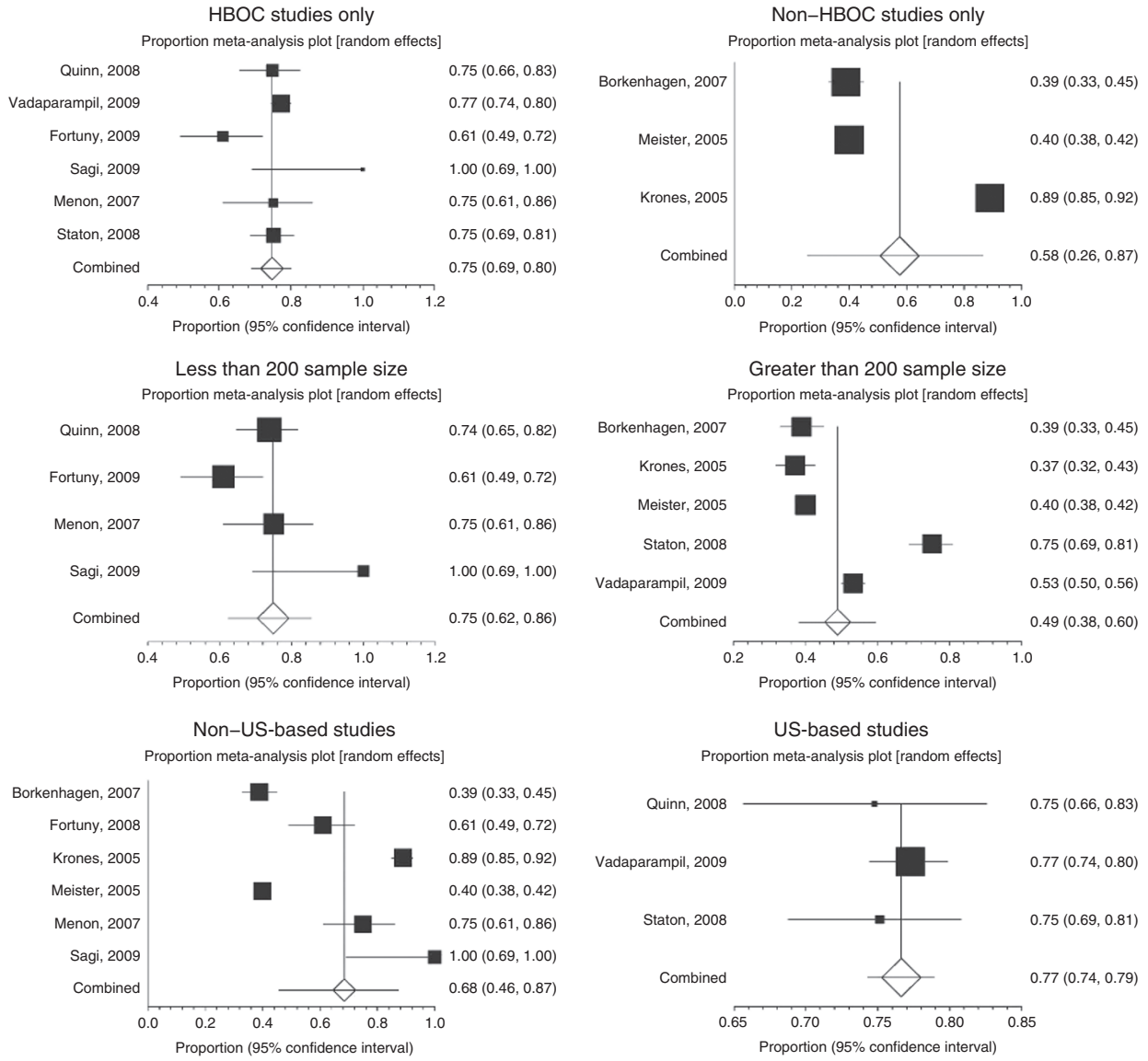

Figure 3 Sensitivity analyses: acceptability of PGD for other high-risk consumers. HBOC, hereditary breast and ovarian cancer; PGD, preimplantation genetic diagnosis.

average, do not believe that a benefit of PGD is avoiding pregnancy termination if it was found that gene mutations had been passed on. There was a statistically significant heterogeneity in the included studies for the outcome of knowledge of PGD (I^2 = 81.8%; P < 0.0041).

Use of PGD due to a concern for future offspring. Data on respondents who indicated they would use PGD themselves specifically due to a concern for future offspring were extractable in 69% (9/13) of studies.[11,20,21,31,34–37,40] The pooled response was 50% (95% CI, 0.54–0.85) indicating that half the participants who would personally use PGD would do so because of a concern for passing on the risk of hereditary cancer to their offspring. There was statistically significant heterogeneity in the included studies for the outcome of knowledge of PGD (I^2 = 99.5%; P < 0.0001).

Ethical implications. Data on respondents indicating that there are ethical concerns to be considered regarding PGD were extractable in 62% (8/13) of studies.[11,20,31,33,34,36,39,40] The pooled response was 33% (95% CI, 20–46%) indicating that a majority of respondents, on average, do not believe there are ethical concerns regarding testing embryos via PGD. There was a statistically significant heterogeneity in the included studies for the outcome of knowledge of PGD (I^2 = 97.7%; P < 0.0001).

Cost. Data on respondents indicating that the cost of PGD is a barrier to the acceptability of the procedure were extractable in 39% (5/13) of studies.[20,31,34,36,37] The pooled response was 29% (95% CI, 16–44%) indicating that a majority of respondents, on average, do not believe that the costs associated with PGD prohibit finding PGD acceptable for the use of hereditary cancers. There was a statistically significant heterogeneity in the

included studies for the outcome of knowledge of PGD (I^2 = 93.5%; $P < 0.0001$).

Additional analyses. To assess the robustness of our findings and explore the reasons behind heterogeneity, we performed additional sensitivity analyses for the outcomes "personal acceptability of PGD" and the "acceptability of PGD to be used by other high-risk consumers," in relation to study location, sample size, and cancer type.

There was no difference in study location and personal acceptability of PGD distinguished between US and non–US-based studies (39% and 36%, respectively). Forty-six percent (6/13) of studies[11,20,21,31–33] recruited participants with a high risk of HBOC only. These studies showed an overall 33% personal acceptability of PGD similar to 30% of participants at high-risk for cancer other than HBOC. Sample size seemed to impact personal acceptability, as trials completed with a sample size of <200 participants[11,33,34,36,37] showed 47% acceptability, compared with studies with sample sizes of more than 200 participants at 29%.[20,21,32,35,38–40]

For the outcome of the acceptability of PGD to be used by other high-risk consumers, studies performed in the United States[20,21,34] did not show a large difference from non–US-based studies[11,31,33,38–40] (68% acceptability vs. 77%). Studies that recruited only those at risk for HBOC[11,20,31,33,34] were found to have an overall 75% acceptability for the use of PGD by other high-risk consumers, which was slightly higher than studies with participants at high-risk for cancer other than HBOC at 58%.[38–40] Sample size again impacted the acceptability of PGD for use by other high-risk consumers showing that studies with samples sizes <200[11,31,33,34] reported 75% acceptability compared similar to 49% when the sample size was more than 200.[20,21,38–40]

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis on the views of PGD from the perspectives of individuals at high-risk for hereditary cancer. The results from this meta-analysis show that levels of knowledge of PGD are low among individuals who are at risk for hereditary cancer. On average, only 35% of individuals in the studies reviewed had knowledge of PGD; however, this only shows that such respondents have heard of PGD before and does not assess what they actually know about PGD. Knowledge and acceptability of PGD could not be correlated as only one study[20] evaluated this, and respondents who indicated both a positive acceptability and high knowledge is otherwise unknown throughout the other included studies.

Vadaparampil et al.[20] found that among respondents who would consider PGD (n = 318), about 47% had heard of PGD before the study. Among respondents who would not consider PGD (n = 367), <30% were aware before the study. Both showed a $P < 0.005$ indicating statistical significance. Meister et al.[40] found that approximately 60% of high-risk respondents were unaware of PGD before the study and 50% had incorrect assumptions about what PGD is capable of diagnosing. Half the respondents overestimated the ability of PGD and assumed this procedure can detect any and all disease. PGD cannot detect abnormalities in all chromosomes and may also result in false-positive diagnoses. [41] Douma et al.[35] found that 84% of 157 FAP patients of childbearing age (<40) reported PGD was not discussed in any clinical setting. Twenty percent indicated they would like more information on this technology. This lack of awareness is likely due to the fact that PGD was not used in the Netherlands for FAP diagnoses during the time of the study; however, one respondent had used PGD in another country.

Personal acceptability of PGD for those at high-risk for cancer was found to be most impacted by sample size. Overall, studies with sample sizes <200 showed a 38% higher personal acceptability than studies with larger sample sizes. Similarly, smaller sample sizes showed higher acceptability for PGD use by other high-risk consumers. This may be due to the gender of participants as 75% (3/4) of studies[31,33,34] with <200 participants recruited females only.[20] Only 20% (1/5) of studies with more than 200 participants recruited females only. This gender difference in larger studies may account for higher acceptability of PGD for others as opposed to smaller studies with male and female perspectives. Some studies assessed the association between personal acceptability of PGD and demographic characteristics of religion, education, and personal history of cancer; however, we did not have independent patient data to run subgroup analyses.

Although studies investigating the perceptions of populations at high-risk for cancer are limited, other studies have assessed the general public's view of using PGD for hereditary cancer. Public attitudes in Britain showed a higher approval of PGD for hereditary cancer versus sex selection (34% vs. 9%).[42] In 2004, the Hopkins Genetics and Public Policy Center surveyed more than 4,000 Americans regarding PGD for medical and non-medical reasons. Although <30% had prior knowledge of PGD, >60% of men and women approved of PGD for identification of an early onset and fatal disease.[43] Similar issues between consumers at high-risk for cancer and the general public have been cited as a fear of the unknown, ethical slippery slopes, and regulation of medical histories.[11]

Acceptability of PGD among high-risk consumers

Individuals who show a positive attitude toward the availability of PGD for others are more likely to consider using PGD for themselves.[20] From the available literature, *BRCA1/2* carriers comprise the largest group for PGD consumer-focused research. Among these, acceptance of PGD for *BRCA1/2* carriers was inconsistent. Three studies indicated a majority in favor of PGD at 88%, 75%, and 90%,[20,31,36] one indicated a minority in favor of PGD at 33%,[32] while the remaining two had approximately a 50% acceptability of PGD.[11,33]

Concern for future offspring seems to be the most cited factor influencing the acceptability of PGD for hereditary cancers.[11,20] Staton et al.[21] found that approximately 88% of

respondents reported frequently worrying about transmitting the mutation to their children, and 75% felt that PGD should be an option offered to other *BRCA1/2* carriers. Fortuny et al.[11] found that 36% of participants indicated they would have children regardless of a positive or negative result, while 12% would not have children if they received positive results, and 30% preferred adoption if they received positive results. Of those who planned to have children, 48% indicated they would consider PGD in the event of a positive result. In the study of *BRCA1/2* carriers by Menon et al.,[31] 38% of women who had completed their families indicated they would have used PGD if it had been available during the period of their childbearing years. Similarly, of 132 *BRCA1/2* carriers who indicated they desired to have more children, 40% viewed PGD as an acceptable option.[20]

Women who have a highly positive attitude toward PGD have been found more likely to report greater feelings of guilt toward their future children.[20,35,37] In the qualitative analysis of survey responses from 446 *BRCA1/2* carriers by Quinn et al.[32], 38% of respondents felt that not testing embryos was "irresponsible." This group of women felt that individuals with a genetic mutation have an obligation to reduce the likelihood that future children would experience negative consequences from this inheritance. Staton et al.[21] report that approximately 88% of respondents reported frequently worrying about transmitting the mutation to their children.

Beyond consumers at risk for HBOC, consumers at risk for developing FAP have reported similar concerns regarding childbearing. FAP has been reported to severely impact the lives of high-risk populations, and 35% of consumers reported that having a predisposition for FAP impacts their decisions on childbearing. Here, 90% of respondents said they would consider using PGD for FAP, even though only 25% indicated having a prior knowledge of PGD.[36]

Despite the technology available that can determine an embryo's risk of developing a hereditary cancer, some consumers have cited ethical implications as a barrier to using this procedure. Sagi et al.[33] reported that some carriers who oppose PGD citied the specific concern about PGD interfering with the IVF process. The majority of studies showed that 33% of respondents cited ethical concerns over the use of PGD, even among respondents who were in favor of the procedure. Despite this, families with children born from PGD were found to have a higher affection toward each other than families with natural born babies.[44] This is an important facet for high-risk consumers to consider as some may be reluctant to use PGD due to the clinical nature of conception.

The results from this systematic review show that study characteristics are not consistent and that aspects of quality reporting are low. Twenty-three percent (3/13) of studies[20,39,40] did not report the response rate of participants, only the final number. In addition, ascertaining mean ages for all 13 studies was not possible, as 23% (3/13) of studies[20,34,39] did not indicate specific averages or age range. Furthermore, the sample sizes greatly varied, the smallest study enrolling 10 participants,[33] while the largest study enrolling 2,110 participants.[38] In general, it is difficult to ascertain comprehensive results due to the variability between each study that assessed similar outcomes.

Similar studies assessing acceptability of PGD from the consumer perspective have shown a majority approval of PGD for genetic disease in general.[45–48] Roberts and Franklin[49] offer one of the few reports investigating factors in decision-making when using PGD and patients' choices made after genetic diagnoses are made. They found that patients make assessments before and throughout the entire PGD process including assessments of the costs of procedure and how their decisions are negotiated within familial and societal contexts, which parallels the outcomes of the meta-analysis. An additional source of discrepancy about PGD for hereditary cancers versus other genetic disease is the concept of increased susceptibility versus inevitability.[20,50] FAP is an early-onset disease which may influence testing at a young age,[51] compared with *BRCA* testing which is typically not recommended before the age of 25 years.[52]

A 2009 study showed that less than half of clinics surveyed that perform PGD and require genetic counseling assessed how well patients understood the information disclosed during a counseling session.[53] Thus, one approach to informing high-risk consumers about PGD and the associated risks and benefits may be through the development of standardized protocols to disseminate consistent, accurate information and support patients' psychological concerns.[54] Currently, the United States has no guidelines or consumer education standards on PGD for hereditary cancer.[55]

This systematic review has limitations. We performed searches of only standardized databases (PubMed, Cochrane, and PsychInfo); therefore, the 13 included studies may not be absolute. Some studies were not clear when defining someone at "high-risk" and the research team had to determine if this included those at high-risk for hereditary cancer only. It is possible that some study samples were mixed with those at high-risk for hereditary cancer and those at high-risk for passing on other genetic disorders. The study by Quinn et al.[32] is a qualitative analysis of free text comments from participants in web-based survey by Vadaparampil et al.[20]; therefore, these numbers were not included in the meta-analyses to prevent duplication of study subjects. However, it is unknown if respondents leaving free text comments also completed each question of the quantitative survey; therefore, some data may have been missed in the meta-analyses. In addition, although the date range included all articles between 1992 and 2009, the included trials were conducted between 2005 and 2009. Because of this narrow time frame, studies could not be divided into intervals and therefore a meta-analysis according to time periods was not performed.

Correlations between outcomes such as knowledge and personal acceptability, knowledge and generalized acceptability, and acceptability and concern for future offspring could not be assessed as these data were not accounted for by at least three studies.

CONCLUSION

The current body of literature that focuses on high-risk consumers' perceptions of PGD for hereditary cancer is limited, which is evidenced by the quantity of eligible articles for this systematic review ($N = 13$). Although the availability of PGD for certain cancer predisposing conditions varies by country and facility, the psychosocial issues that high-risk consumers face over certain issues such as embryo selection are similar.

The findings from our review suggest overall low levels of awareness but moderate to high levels of acceptability among individuals concerned about hereditary cancer risk. All included studies were conducted between 2005 and 2009 (although the search was done for years 1992 to 2009). For this reason, we were unable to perform a sensitivity analysis according to year; however, the wide variation in consumers' perceptions of PGD presented during this narrow time frame reinforces the need to educate high-risk consumers about PGD to facilitate informed decision-making. Couples and individuals may have different experiences undergoing PGD depending on the clinic they use, as many do not have a standardized set of procedures for referral, counseling, and informed consent for patients who may seek PGD. Health professionals are an important component of increasing knowledge about PGD, and high-risk consumers should have the option of making informed decisions. This can only be accomplished when awareness is present.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene* 2004;23:6445–6470.
2. Lichtenstein P, Holm NV, Verkasalo PK, *et al*. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78–85.
3. Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol* 2005;23:276–292.
4. Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. *Lancet* 2004;363:1633–1641.
5. Ogilvie CM, Braude PR, Scriven PN. Preimplantation genetic diagnosis–an overview. *J Histochem Cytochem* 2005;53:255–260.
6. Baruch S, Kaufman D, Hudson KL. Genetic testing of embryos: practices and perspectives of US *in vitro* fertilization clinics. *Fertil Steril* 2008;89:1053–1058.
7. Simpson JL. Preimplantation genetic diagnosis at 20 years. *Prenat Diagn* 2010;30:682–695.
8. McArthur SJ, Leigh D, Marshall JT, de Boer KA, Jansen RP. Pregnancies and live births after trophectoderm biopsy and preimplantation genetic testing of human blastocysts. *Fertil Steril* 2005;84:1628–1636.
9. Friedman LC, Kramer RM. Reproductive issues for women with BRCA mutations. *J Natl Cancer Inst Monogr* 2005;2005:83–86.
10. Smith KR, Ellington L, Chan AY, Croyle RT, Botkin JR. Fertility intentions following testing for a BRCA1 gene mutation. *Cancer Epidemiol Biomarkers Prev* 2004;13:733–740.
11. Fortuny D, Balmaña J, Graña B, *et al*. Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort. *Hum Reprod* 2009;24:1000–1006.
12. Allen C, Reardon W. Assisted reproduction technology and defects of genomic imprinting. *BJOG* 2005;112:1589–1594.
13. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and *in vitro* fertilization. *N Engl J Med* 2002;346:725–730.
14. Desmyttere S, Bonduelle M, Nekkebroeck J, Roelants M, Liebaers I, De Schepper J. Growth and health outcome of 102 2-year-old children conceived after preimplantation genetic diagnosis or screening. *Early Hum Dev* 2009;85:755–759.
15. Liebaers I, Desmyttere S, Verpoest W, *et al*. Report on a consecutive series of 581 children born after blastomere biopsy for preimplantation genetic diagnosis. *Hum Reprod* 2010;25:275–282.
16. Desmyttere S, De Schepper J, Nekkebroeck J, *et al*. Two-year auxological and medical outcome of singletons born after embryo biopsy applied in preimplantation genetic diagnosis or preimplantation genetic screening. *Hum Reprod* 2009;24:470–476.
17. Jones BA, McMahon CA. Social representations of stem cell research and preimplantation genetic diagnosis. *Reprod Biomed Online* 2003;7:268–275.
18. Klitzman R, Appelbaum PS, Chung W, Sauer M. Anticipating issues related to increasing preimplantation genetic diagnosis use: a research agenda. *Reprod Biomed Online* 2008;17(suppl 1):33–42.
19. Miedzybrodzka Z, Templeton A, Dean J, Haites N, Mollison J, Smith N. Preimplantation diagnosis or chorionic villus biopsy? Women's attitudes and preferences. *Hum Reprod* 1993;8:2192–2196.
20. Vadaparampil ST, Quinn GP, Knapp C, Malo TL, Friedman S. Factors associated with preimplantation genetic diagnosis acceptance among women concerned about hereditary breast and ovarian cancer. *Genet Med* 2009;11:757–765.
21. Staton AD, Kurian AW, Cobb K, Mills MA, Ford JM. Cancer risk reduction and reproductive concerns in female BRCA1/2 mutation carriers. *Fam Cancer* 2008;7:179–186.
22. Quinn GP, Vadaparampil ST, Tollin S, *et al*. BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. *Fertil Steril* 2010;94:2473–2475.
23. Quinn GP, Vadaparampil ST, Jacobsen PB, Knapp C, Keefe DL, Bell GE. Frozen hope: fertility preservation for women with cancer. *J Midwifery Womens Health* 2010;55:175–180.
24. Stuart A, Ord J. *Kendall's Advanced Theory of Statistics*. Edward Arnold: London, 1994.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–1101.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
28. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676–680.
29. Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) explanation and elaboration. *Epidemiology* 2007;4:805–835.
30. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W65–W94.
31. Menon U, Harper J, Sharma A, *et al*. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. *Hum Reprod* 2007;22:1573–1577.
32. Quinn GP, Vadaparampil ST, King LM, Miree CA, Friedman S. Conflict between values and technology: perceptions of preimplantation genetic diagnosis among women at increased risk for hereditary breast and ovarian cancer. *Fam Cancer* 2009;8:441–449.
33. Sagi M, Weinberg N, Eilat A, *et al*. Preimplantation genetic diagnosis for BRCA1/2–a novel clinical experience. *Prenat Diagn* 2009;29:508–513.

34. Quinn G, Vadaparampil S, Wilson C, *et al*. Attitudes of high-risk women toward preimplantation genetic diagnosis. *Fertil Steril* 2009;91:2361–2368.
35. Douma KF, Aaronson NK, Vasen HF, Verhoef S, Gundy CM, Bleiker EM. Attitudes toward genetic testing in childhood and reproductive decision-making for familial adenomatous polyposis. *Eur J Hum Genet* 2010;18:186–193.
36. Kastrinos F, Stoffel EM, Balmaña J, Syngal S. Attitudes toward prenatal genetic testing in patients with familial adenomatous polyposis. *Am J Gastroenterol* 2007;102:1284–1290.
37. Lammens C, Bleiker E, Aaronson N, *et al*. Attitude towards pre-implantation genetic diagnosis for hereditary cancer. *Fam Cancer* 2009;8:457–464.
38. Borkenhagen A, Brähler E, Wisch S, Stöbel-Richter Y, Strauss B, Kentenich H. Attitudes of German infertile couples towards preimplantation genetic diagnosis for different uses: a comparison to international studies. *Hum Reprod* 2007;22:2051–2057.
39. Krones T, Schlüter E, Manolopoulos K, *et al*. Public, expert and patients' opinions on preimplantation genetic diagnosis (PGD) in Germany. *Reprod Biomed Online* 2005;10:116–123.
40. Meister U, Finck C, Stöbel-Richter Y, Schmutzer G, Brähler E. Knowledge and attitudes towards preimplantation genetic diagnosis in Germany. *Hum Reprod* 2005;20:231–238.
41. Goossens V, De Rycke M, De Vos A, *et al*. Diagnostic efficiency, embryonic development and clinical outcome after the biopsy of one or two blastomeres for preimplantation genetic diagnosis. *Hum Reprod* 2008;23:481–492.
42. Marteau T, Michie S, Drake H, Bobrow M. Public attitudes towards the selection of desirable characteristics in children. *J Med Genet* 1995;32:796–798.
43. Genetics and Public Policy Center. Americans deeply divided about use of genetic technologies in reproduction; first detailed survey probes public's views on 'designer babies' (Princeton Survey Research Associates website) 2004. <http://www.dnapolicy.org/images/reportpdfs/PublicAwarenessAndAttitudes.pdf>. Accessed 28 January 2010.
44. Banerjee I, Shevlin M, Taranissi M, *et al*. Health of children conceived after preimplantation genetic diagnosis: a preliminary outcome study. *Reprod Biomed Online* 2008;16:376–381.
45. Pergament E. Preimplantation diagnosis: a patient perspective. *Prenat Diagn* 1991;11:493–500.
46. Chamayou S, Guglielmino A, Giambona A, *et al*. Attitude of potential users in Sicily towards preimplantation genetic diagnosis for beta-thalassaemia and aneuploidies. *Hum Reprod* 1998;13:1936–1944.
47. Shahine LK, Kuppermann M, Davis G, Creasman J, Cedars MI. Patient willingness to participate in a clinical trial with preimplantation genetic diagnosis. *Fertil Steril* 2008;89:879–884.
48. Snowdon C, Green JM. Preimplantation diagnosis and other reproductive options: attitudes of male and female carriers of recessive disorders. *Hum Reprod* 1997;12:341–350.
49. Roberts C, Franklin S. Experiencing new forms of genetic choice: findings from an ethnographic study of preimplantation genetic diagnosis. *Hum Fertil (Camb)* 2004;7:285–293.
50. Lavery SA, Aurell R, Turner C, Taylor DM, Winston RM. An analysis of the demand for and cost of preimplantation genetic diagnosis in the United Kingdom. *Prenat Diagn* 1999;19:1205–1208.
51. *John Hopkins Guide for Patients and Families*. Familial adenomatous polyposis. 1994. (Mid-Atlantic Cancer Genetics Network (MACGN)). 1994. Booker S, Celano P, Cox D, *et al*. 1994. <http://www.macgn. org/cc_fap1.html>. Accessed 1 February 2010.
52. Lynch HT, Lemon SJ, Durham C, *et al*. A descriptive study of BRCA1 testing and reactions to disclosure of test results. *Cancer* 1997;79:2219–2228.
53. McGowan ML, Burant CJ, Moran R, Farrell R. Patient education and informed consent for preimplantation genetic diagnosis: health literacy for genetics and assisted reproductive technology. *Genet Med* 2009;11:640–645.
54. Kalfoglou AL, Scott J, Hudson K. Attitudes about preconception sex selection: a focus group study with Americans. *Hum Reprod* 2008;23:2731–2736.
55. Hudson KL. Preimplantation genetic diagnosis: public policy and public attitudes. *Fertil Steril* 2006;85:1638–1645.