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# Attitudes toward childbearing and prenatal testing in individuals undergoing genetic testing for Lynch Syndrome

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**Abstract** To examine attitudes toward childbearing and prenatal genetic testing among individuals at risk for Lynch Syndrome (LS), the most common type of hereditary colorectal cancer. Individuals undergoing clinical genetic testing for mismatch repair (MMR) gene mutations completed written questionnaires before and after testing. 161 of 192 (84%) eligible individuals participated in the study. Mean age was 46 years (range 20–75), 71% were female, 53% had a personal diagnosis of cancer, and 68% had children. Eighty percent worried about their children's risk for developing cancer; however only 9% reported their decision to have children was affected by their family history of cancer. When asked whether providing prenatal testing to carriers of MMR gene mutations was ethical, 66% (86/130) of respondents agreed/strongly agreed, 25% (32) were neutral and 9% (12) disagreed/strongly disagreed. Of 48 individuals planning to have children in the future, 57% (27) intended to have children regardless of their genetic test result. If found to carry a MMR gene mutation that confirmed LS, 42% (20) would consider prenatal testing for a future pregnancy and 20% (7/35) of women would consider having children earlier in order to have prophylactic surgery to reduce their risk for gynecologic cancers. Individuals undergoing genetic testing for LS may utilize test results to make reproductive decisions. Clinicians should be prepared to discuss options of reproductive genetic technologies during counseling of LS patients of childbearing age.

**Keywords** Lynch syndrome · Prenatal testing · Preimplantation genetic diagnosis · Family · Genetic testing · Genetic counseling

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## Introduction

Lynch Syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is the most common type of hereditary colorectal cancer (CRC). Individuals with LS have a high lifetime risk of CRC which approaches 70% in the absence of colonoscopic surveillance and are also predisposed to other extracolonic tumors, including endometrial and ovarian cancers [1–4]. LS is caused by germline mutations in DNA mismatch repair (MMR) genes and genetic testing for *MLH1, MSH2, MSH6, EPCAM* and *PMS2* genes is now commercially available. Genetic testing is used to identify at-risk individuals who require specialized cancer surveillance, which can reduce cancer incidence and improve survival among individuals with familial CRC syndromes [5–7].

Prenatal testing for genetic conditions has been performed for decades and is routinely offered to screen for inherited diseases which cause significant morbidity and mortality in children, such as cystic fibrosis [8–10] and Tay-Sachs [10, 11]. Prenatal testing technologies currently

available include preimplantation genetic diagnosis (PGD) and prenatal diagnostic testing (PND), which can identify whether the gene mutation is present in the embryo before or after uterine implantation, respectively [9].

As clinical genetic testing has become more available, interest in assisted reproductive technologies has grown among individuals affected with familial cancer syndromes [3, 12–14]. Prenatal testing has been used in highly penetrant autosomal dominant cancer syndromes including Li-Fraumeni syndrome (LFS), [15–17]familial adenomatous polyposis (FAP), [12, 18–21]and multiple endocrine neoplasia, [22] as well as in variably penetrant syndromes such as hereditary breast ovarian cancer (HBOC), [23–26] and hereditary retinoblastoma [27–30]. In this study we sought to examine the attitudes toward childbearing and prenatal genetic testing among individuals undergoing genetic evaluation for Lynch syndrome (LS).

## Methods

Individuals undergoing clinical genetic testing for LS at the Dana-Farber Cancer Institute (Boston, MA) between November 2003 and November 2009, were invited to participate in a longitudinal questionnaire study examining cancer risk awareness, health behaviors, and attitudes toward genetic testing. Patients were considered eligible for the study if they were at least 18 years of age and had a personal or family history meeting clinical criteria for genetic evaluation for LS [31]. Study participants completed a series of questionnaires prior to genetic testing (pre-test), at 3 months and 1 year after genetic testing.

### Study instruments

The study questionnaires were developed at the Dana-Farber Cancer Institute and included questions used in previous studies with individuals with LS, HBOC syndrome and other populations with inherited conditions [32–41]. The pre-test questionnaire elicited standard demographic data as well as information about personal and family history of cancer, health and cancer screening behaviors and cancer risk perception. In addition, the instrument contained questions assessing individuals' motivations for undergoing genetic testing, plans for having children and whether genetic test results would have an impact on decisions regarding childbearing.

The questions pertaining to prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) had been used in previous studies with individuals with FAP and patients undergoing genetic testing for HBOC [40, 42]. A brief introductory description of PND and PGD was provided (Table 1). Participants were asked to rank (on a five-point Likert scale) the degree to which they agreed/disagreed with statements that it is ethical to provide PGD or PND to individuals with a known genetic mutation for LS (Table 2). Participants were asked whether a "positive" genetic test result (confirming the diagnosis of Lynch Syndrome) would affect their decision to have children (response choices included 'yes', 'no', 'I don't know' and 'N/A- I am not considering having children in the future'). Participants who indicated they were considering (more) children were asked whether receiving a positive genetic test result would change their decision to have children or consider adoption and whether they would consider prenatal testing using either PGD or PND (Table 3). Responses were selected from a five-point Likert scale ranging from 'strongly agree' to 'strongly disagree'.

The study was approved by the Institutional Review Board of the Dana-Farber Cancer Institute/Harvard Cancer Center and informed consent was obtained from all subjects.

### Statistical analysis

Questionnaire data were scanned and incorporated into computerized data sets for analyses using statistical software programs (SAS, Version 9.1). Responses to the question "Do you think it is ethical to provide PGD or PND to individuals with a known genetic mutation for LS?" were dichotomized as 'agree/strongly agree/neutral' versus 'not agree' (disagree or strongly disagree). Responses to questions of whether participants would consider PGD or PND if their test result showed they carried a genetic mutation associated with LS were dichotomized as 'agree/strongly agree' versus 'not agree' (neutral, disagree or strongly disagree). Because of the small number of subjects considering having children in the future, individuals who answered agree/strongly agree that they would consider either PGD and/or PND were grouped together and classified as considering prenatal testing. The associations of individual dichotomous variables (subject characteristics including gender, personal history of cancer, having children) with the outcomes (including interest in prenatal testing and opinion on ethics of prenatal testing) were explored using Fisher's Exact test and quantified using odds ratios (OR). A $P$ value of $< 0.05$ was considered statistically significant.

## Results

Out of 192 individuals invited to participate in the study, 161 (84%) completed the study questionnaire prior to genetic testing. The overall mean age of participants was 46.1 years with an age range of 20–75 years. 115 (71%)

**Table 1** Description of prenatal testing technologies

| |
|---|
| **Prenatal diagnosis (PND)** can be performed when a woman is *already pregnant* and can be used to test the pregnancy for a number of disorders, including genetic mutations which have been identified in a family. The test is performed using amniocentesis and can be performed during the first 10–18 weeks of pregnancy. Having the result of the prenatal test, the woman can decide whether or not to continue the pregnancy. |
| **Preimplantation Genetic Diagnosis (PGD)** can be performed *before a woman becomes pregnant* and can be performed using in vitro fertilization (IVF). IVF is a reproductive technology in which eggs and sperm are brought together in a laboratory dish to allow the sperm to fertilize an egg and create embryos, which can then be implanted into a woman. Before an embryo is implanted, one of the cells can be tested for gene mutations so that only the embryos that do not contain mutations are implanted in the woman's uterus. |

**Table 2** Questions on ethics of prenatal testing

| | | | | |
|---|---|---|---|---|
| "Do you think it is ethical to provide the following procedures to individuals with a known genetic mutation for Lynch Syndrome?" | | | | |
| (a) I think it is ethical to provide prenatal diagnosis (PND) to individuals with a known genetic mutation for Lynch Syndrome | | | | |
| (b) I think it is ethical to provide preimplantation genetic diagnosis (PGD) to individuals with a known genetic mutation for Lynch Syndrome | | | | |
| Answer scale: | | | | |
| Strongly disagree | Disagree | Neutral | Agree | Strongly agree |

**Table 3** Questions on effect of genetic testing on reproductive decision making

| | | | | |
|---|---|---|---|---|
| "If you were considering having (more) children, please indicate your agreement with each of the following statements assuming you were to receive a positive genetic test result." | | | | |
| N/A—I am not considering having children in the future | | | | |
| (a) I would decide to have children, but I would consider prenatal diagnosis (PND) | | | | |
| (b) I would decide to have children, but I would consider preimplantation genetic diagnosis (PGD) | | | | |
| (c) I would consider having children earlier than planned so I could then have prophylactic surgery | | | | |
| (d) I would consider adoption | | | | |
| (e) I would decide *not* to have children | | | | |
| (f) I would decide to have children *regardless* of my genetic test result | | | | |
| (g) I would decide to have children *only* if I test negative | | | | |
| Answer scale: | | | | |
| Strongly disagree | Disagree | Neutral | Agree | Strongly agree |

subjects were women. Nearly all (95%) subjects classified their race as white. Half (53%) had previously been diagnosed with cancer and 3 (1.8%) were undergoing genetic testing for a LS mutation previously identified in a family member. 129/161 (80%) responders said they were worried about their children's cancer risk given their own family history. 109/161 (68%) responders already had children and only 14/161 (9%) said they had decided not to have (more) children because of their familial cancer risk.

## Baseline attitudes regarding prenatal testing for lynch syndrome

130 of 161 (80%) participants who completed baseline questionnaires answered the questions regarding prenatal testing. Although the 31 non-responders were significantly older than responders (mean age 53.2 vs. 45.6 years, $P < 0.05$), there were no other demographic differences between subjects who did and did not answer the questions in this section. Before receiving the results of their genetic test, subjects were asked whether they felt it would be ethical to provide some type of prenatal testing for individuals with mutations associated with Lynch Syndrome and 86 (66%) responders strongly agreed/agreed, 32 (25%) were neutral and only 12 (9%) disagreed/strongly disagreed. There were no significant differences in demographic characteristics between those whose response was "agree" or "neutral" and those who disagreed that providing prenatal testing was ethical (Table 4). Of those who believed providing prenatal testing was ethical, 72/86 (84%) agreed with offering both PND and PGD, while 9 (10%) agreed with providing PND but not PGD and 5 (6%) agreed with providing PGD but not PND.

## Plans for future childbearing

Prior to genetic testing, subjects were asked if they were considering having children in the future and how

**Table 4** Subject characteristics grouped by their response to the question: Do you think it is ethical to provide PND/PGD to individuals with a known genetic mutation for Lynch Syndrome/HNPCC? (N = 130)

| Characteristic | Agree/strongly agree | | Disagree/strongly disagree | | Neutral | |
|---|---|---|---|---|---|---|
| | N | Row % | N | Row % | N | Row % |
| All subjects | 86 | 66.2 | 12 | 9.2 | 32 | 24.6 |
| Mean age in years (SD) | 46.8 (12.4) | – | 45.8 (13.0) | – | 42.5 (8.4) | – |
| Gender | | | | | | |
| Female | 59 | 64.8 | 6 | 6.6 | 26 | 28.6 |
| Male | 27 | 69.2 | 6 | 15.4 | 6 | 15.4 |
| *Marital status | | | | | | |
| Married | 56 | 65.9 | 9 | 10.6 | 20 | 23.5 |
| Not Married | 24 | 64.9 | 3 | 8.1 | 10 | 27.0 |
| Race | | | | | | |
| White | 82 | 66.7 | 12 | 9.8 | 29 | 23.6 |
| Other race | 4 | 57.1 | 0 | 0 | 3 | 42.9 |
| Personal history of cancer | | | | | | |
| Yes | 46 | 68.7 | 5 | 7.4 | 16 | 23.9 |
| No | 40 | 63.5 | 7 | 11.1 | 16 | 25.4 |
| Already have children | | | | | | |
| Yes | 57 | 65.5 | 10 | 11.5 | 20 | 23.0 |
| No | 29 | 67.4 | 2 | 4.7 | 12 | 27.9 |
| **Education | | | | | | |
| College graduate | 58 | 67.4 | 11 | 12.8 | 17 | 19.8 |
| Not college graduate | 22 | 64.7 | 1 | 2.9 | 11 | 32.4 |
| ***Annual household income | | | | | | |
| <$50,000 | 60 | 63.2 | 10 | 10.5 | 25 | 26.3 |
| ≥$50,000 | 17 | 70.8 | 2 | 8.3 | 5 | 20.8 |

*PND* prenatal diagnosis, *PGD* preimplantation genetic diagnosis, *HNPCC* (Lynch Syndrome) hereditary non-polyposis colorectal cancer

* missing 8 subjects, ** missing 10 subjects, *** missing 11 subjects

receiving a positive genetic test result might affect their plans. Forty-eight subjects indicated that they were considering having children; of these 27 (56%) indicated they planned to have children regardless of the result of their genetic test. Among women considering a future pregnancy, seven of 35 (20%) said that if their genetic test showed they carried a mutation they would plan to have children earlier in order to proceed with prophylactic surgery to reduce their risk for gynecologic cancers associated with LS. Thirteen subjects (27%) indicated they would consider adoption in the setting of a positive genetic test result. Only five individuals (10%) said they would decide not to have children if they were found to carry a MMR gene mutation.

When asked about prenatal testing for Lynch Syndrome, 20/48 (42%) subjects considering a future pregnancy agreed/strongly agreed that they would consider prenatal testing if they were found to carry a MMR gene mutation (10 would consider PGD and/or PND, 9 would consider only PND, and 1 would consider only PGD). Twenty (42%) respondents indicated they would not consider prenatal testing and 8 (17%) were undecided or neutral. Comparison of characteristics of subjects who would and would not consider prenatal testing for Lynch Syndrome appears in Table 5. Individuals who would consider prenatal testing were significantly younger than those who would not (mean age 35 vs. 42 years, $P = 0.02$). Interest in prenatal testing was also higher among subjects who were not married and among those who reported annual household incomes below $50,000. Interest in prenatal testing appeared to be less among individuals who already had children when compared with those without children, although this difference did not achieve statistical significance ($P = 0.08$).

## One-year follow up

Follow up questionnaires completed 1 year after disclosure of genetic test results were available for 35 of 48 (73%) subjects who were considering a future pregnancy. One individual who had tested negative for the familial MMR mutation reported the birth of a child. Two out of 9 (22%)

**Table 5** Characteristics of individuals considering a future pregnancy, grouped by their intention to consider PND/PGD if found to carry an MMR gene mutation (N = 48)

| Characteristic | Strongly agree/agree to consider PND/PGD | | Strongly disagree/disagree/neutral to consider PND/PGD | | |
|---|---|---|---|---|---|
| | N | Row% | N | Row % | *P* |
| All subjects | 20 | 41.7 | 28 | 58.3 | |
| Mean age in years (SD) | 35.0 (10.5) | – | 42.0 (9.7) | – | 0.02 |
| Gender | | | | | |
| Female | 17 | 48.6 | 18 | 51.4 | 0.18 |
| Male | 3 | 23.1 | 10 | 76.9 | |
| *Marital status | | | | | |
| Married | 7 | 25.9 | 20 | 74.1 | 0.03 |
| Not Married | 12 | 60.0 | 8 | 40.0 | |
| Personal history of cancer | | | | | |
| Yes | 10 | 58.8 | 7 | 41.2 | 0.13 |
| No | 10 | 32.3 | 21 | 67.7 | |
| Already have children | | | | | |
| Yes | 6 | 27.3 | 16 | 72.7 | 0.08 |
| No | 14 | 53.9 | 12 | 46.1 | |
| *Education | | | | | |
| College graduate | 12 | 37.5 | 20 | 62.5 | 0.75 |
| Not college graduate | 7 | 46.7 | 8 | 53.3 | |
| **Annual household income | | | | | |
| <$50,000 | 9 | 81.8 | 2 | 18.2 | 0.004 |
| ≥$50,000 | 10 | 29.4 | 24 | 70.6 | |

*PND* prenatal diagnosis, *PGD* preimplantation genetic diagnosis, *MMR* mismatch repair gene mutation

* missing 1 subject, ** missing 3 subjects

mutation carriers indicated they were considering using PGD for a future pregnancy.

## Discussion

Hereditary cancer syndromes affect families. Carriers of MMR gene mutations are at increased risk for developing cancer themselves, and have a 50/50 chance of passing on this inherited susceptibility to each of their children. Although most individuals with a family history of cancer would not decide to forego having children, the identification of a heritable gene mutation may influence reproductive decisions. Our findings demonstrate that if found to carry a gene mutation associated with Lynch Syndrome, 42% of individuals contemplating future pregnancies would consider using prenatal testing and one in five women would consider having children earlier in order to proceed with prophylactic surgery to reduce their risk for developing gynecologic cancers. Overall, the majority of individuals undergoing genetic testing for LS felt that it would be ethical to offer prenatal genetic testing (either PGD or PND) to those with pathogenic MMR gene mutations.

The American Medical Association (AMA) Code of Medical Ethics states that prenatal genetic testing is most acceptable "for women or couples whose medical histories or family backgrounds indicate an elevated risk of fetal genetic disorder" [43]. Prenatal testing for genetic conditions has been available for decades and preimplantation genetic diagnosis has been performed for a number of cancer syndromes including hereditary breast ovarian cancer, Li Fraumeni syndrome, neurofibromatosis 1 and 2, Von Hippel Lindau disease, hereditary retinoblastoma, familial adenomatous polyposis (FAP), and Lynch Syndrome, among others [44]. In May 2006, the United Kingdom's Human Fertilisation and Embryology Authority (HFEA) added hereditary breast ovarian and bowel cancer syndromes as conditions for which PGD might be approved, while also noting that indications should be reviewed on a case by case basis [26].

In our previous survey of 20 individuals with FAP, we found that all but 1 indicated they would consider prenatal testing for future pregnancies [40].

The present study, which examines attitudes toward childbearing and reproductive decision-making in individuals at risk for LS, indicates that while most believe it would be ethical to offer prenatal testing to LS mutation

carriers, only 42% of those contemplating a future pregnancy would consider using prenatal testing themselves. Our findings are similar to those of other studies conducted among patients at risk for HBOC. Fortuny et al. used our same study questionnaire in a Spanish cohort of 77 individuals undergoing genetic testing for *BRCA1/2* mutations and found that 48% and 55% of subjects would consider PGD and PND, respectively [42]. In other surveys of women at high risk for HBOC Quinn et al. found that 57% thought PGD was an acceptable option; however only 33% would consider using PGD themselves [45]. Menon et. al. found 75% of BRCA mutation carriers considered PGD acceptable, but only 38% would have used it had it been available [46]. At present there are few data regarding the uptake of PGD and PND for cancer predisposition syndromes. In 2007 the 57 centers enrolled in the European ESHRE PGD consortium reported only 12 cycles for FAP, 1 for HNPCC, and 4 for BRCA1 [47]. The Regional Genetics Service in Manchester, UK reported that 1.8% of FAP and 1% of LS and HBOC carriers were referred to discuss PGD in 2009 [48].

Decisions regarding childbearing are very personal ones and may be influenced by an individual's personal and family history of cancer. While most of the subjects in our study believed prenatal testing would be ethical, only a minority would consider it themselves. In weighing the implications of prenatal testing in the care of families affected by hereditary cancer syndromes, Offit et. al. have suggested the following framework [44] (1) Does the disease have onset in childhood, with risk of death or severe morbidity by early adulthood? (2) What is the penetrance of disease and how severe is the phenotype? (3) Can the risk be reduced through surveillance or preventive surgeries? In this context, our finding that the potential rate of uptake of prenatal testing for Lynch Syndrome is markedly lower than for FAP is not surprising. In contrast to FAP, Lynch syndrome rarely results in childhood morbidity, the penetrance is highly variable, and the risk for CRC can be reduced effectively through frequent colonoscopic surveillance.

Our study is among the first to demonstrate that genetic testing may influence reproductive decision-making for individuals at risk for Lynch Syndrome. However, we recognize our study has several limitations. Subjects were recruited from a single, tertiary-referral cancer genetics clinic and elected to participate in a longitudinal questionnaire study; consequently it is possible their opinions may not be generalizable to other individuals with LS. We did not collect information about participants' religious affiliation, which might influence attitudes regarding prenatal testing and pregnancy termination. The description of PND and PGD provided to subjects was brief and did not include any technical details about the procedures such as potential complications, success rates, or financial cost, which might influence patient decision-making, nor did the questionnaire require subjects to provide reasons why they might favor PGD vs. PND. Finally, the number of subjects contemplating future pregnancies was small and the follow up period was too short to quantify actual uptake or success rates for PGD and PND.

Even so, our findings demonstrate that genetic testing for LS can affect patients' decisions about childbearing and suggest that most feel it is ethical to offer the option of prenatal testing for MMR gene mutation carriers. Although ethical concerns have been raised in recent literature about the "slippery slope of trying to achieve genetic perfection" and "designer babies," [23, 44, 49–51] there have also been "wrongful birth" lawsuits in which parents claim that they were deprived of the opportunity to terminate a pregnancy due to the physician's failure to inform them of the risk of genetic illness in their offspring [44]. A recent survey of patients with FAP of childbearing age found that approximately 84% had no prior information about PGD or PND [52]. The widespread availability of prenatal testing for multiple disease conditions makes it imperative for clinicians to be aware of the existing technology and to be prepared to offer referrals for patients who are interested in learning more about options for prenatal genetic testing [53].

## Conclusion

Our results suggest that a number of men and women at risk for Lynch Syndrome would utilize the information learned from genetic testing in making reproductive decisions. Only a small minority felt that offering prenatal testing for LS would not be ethical. Health care providers should be prepared to discuss the option of assisted reproductive technologies during genetic counseling of individuals with hereditary cancer syndromes, such as LS, who are of childbearing age.

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