Risks of Less Common Cancers in Proven Mutation Carriers With Lynch Syndrome


ABSTRACT

Purpose
Patients with Lynch syndrome are at high risk for colon and endometrial cancer, but also at an elevated risk for other less common cancers. The purpose of this retrospective cohort study was to provide risk estimates for these less common cancers in proven carriers of pathogenic mutations in the mismatch repair (MMR) genes MLH1, MSH2, and MSH6.

Patients and Methods
Data were pooled from the German and Dutch national Lynch syndrome registries. Seven different cancer types were analyzed: stomach, small bowel, urinary bladder, other urothelial, breast, ovarian, and prostate cancer. Age-, sex- and MMR gene–specific cumulative risks (CRs) were calculated using the Kaplan-Meier method. Sex-specific incidence rates were compared with general population incidence rates by calculating standardized incidence ratios (SIRs). Multivariate Cox regression analysis was used to estimate the impact of sex and mutated gene on cancer risk.

Results
The cohort comprised 2,118 MMR gene mutation carriers (MLH1, n = 806; MSH2, n = 1,004; MSH6, n = 308). All cancers were significantly more frequent than in the general population. The highest risks were found for male small bowel cancer (SIR, 251; 95% CI, 177 to 346; CR at 70 years, 12.0; 95% CI, 5.7 to 18.2). Breast cancer showed an SIR of 1.9 (95% CI, 1.4 to 2.4) and a CR of 14.4 (95% CI, 9.5 to 19.3). MSH2 mutation carriers had a considerably higher risk of developing urothelial cancer than MLH1 or MSH6 carriers.

Conclusion
The sex- and gene-specific differences of less common cancer risks should be taken into account in cancer surveillance and prevention programs for patients with Lynch syndrome.

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INTRODUCTION

Lynch syndrome (LS), often also termed hereditary nonpolyposis colorectal cancer (HNPPC), is an autosomal-dominant inherited disorder caused by germline mutations in genes of the DNA mismatch repair (MMR) system. Patients affected by this condition are at a considerably increased risk of developing colorectal and endometrial cancer. In addition, other cancers such as carcinomas of the stomach, small bowel, ovaries, biliary tract, urinary tract, and brain and sebaceous tumors are observed more frequently than in the general population. Reliable estimates of age-, gene-, and sex-specific risks for these less common cancers are important for the design of appropriate surveillance and prevention programs. Specific surveillance measures may be narrowed down and tailored according to age, sex, and endangered target organ. Moreover, cancer risks may be considerably different according to the mutated MMR gene, thus making specific recommendations necessary. Several studies have been published giving risk estimates for a variety of extra-colonic, extra-endometrial cancers, including a large collaborative study combining data of 6,041 proven or probable MLH1 and MSH2 mutation carriers from four LS registries.

In this study we aimed to estimate the risks of less common cancers in patients with a proven mutation in the MMR genes MLH1, MSH2, or MSH6. We were particularly interested in analyzing the risks by sex and mutated MMR gene. Furthermore, we sought to compare the risk estimates with those from the general population. To achieve a sufficient
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number of patients for the analysis, the study was conducted as a joint project of two registries from Germany and the Netherlands.

**Tables and Figures**

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Germany</th>
<th>Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals, n</td>
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<td>1,257</td>
<td>861</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>1,011</td>
<td>657</td>
<td>354</td>
</tr>
<tr>
<td>Female</td>
<td>1,107</td>
<td>600</td>
<td>507</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1968</td>
<td>1969</td>
<td>1966</td>
</tr>
<tr>
<td>MMR gene</td>
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<tr>
<td>MLH1</td>
<td>806</td>
<td>483</td>
<td>323</td>
</tr>
<tr>
<td>MSH2</td>
<td>1,004</td>
<td>650</td>
<td>354</td>
</tr>
<tr>
<td>MSH6</td>
<td>308</td>
<td>124</td>
<td>184</td>
</tr>
<tr>
<td>Affected with cancer</td>
<td></td>
<td></td>
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<tr>
<td>Colon or rectum</td>
<td>1,050</td>
<td>624</td>
<td>426</td>
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<tr>
<td>Endometrium</td>
<td>177</td>
<td>102</td>
<td>75</td>
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<tr>
<td>Stomach</td>
<td>33</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Small bowel</td>
<td>54</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>31</td>
<td>18</td>
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<tr>
<td>Other urothelium</td>
<td>45</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Breast</td>
<td>50</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Ovary</td>
<td>49</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>Prostate</td>
<td>17</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Other cancers*</td>
<td>110</td>
<td>55</td>
<td>34</td>
</tr>
</tbody>
</table>

*CSS, skin, pancreas, kidney, leukemia, lung, gallbladder, thyroid.

**RESULTS**

The study cohort comprised a total of 2,118 individuals with a proven pathogenic mutation in MLH1, MSH2, or MSH6. Table 1 shows the basic characteristics. The proportion of male mutation carriers was significantly higher in the German than in the Dutch cohort (52.3% vs. 41.1%, respectively; P < .001), whereas the age structure was similar (median year of birth, 1957; P = .34). The distribution of the mutated gene was also significantly different between the two registries (P < .001). MSH6 mutation carriers were more frequent in the Dutch than in the German cohort (21.4% vs. 9.9%, respectively). The frequency of patients with colorectal cancer was considerably higher in the German than in the Dutch cohort (65.6% vs. 26.2%).

Figures 1 and 2 show the age-dependent cumulative risks for the seven cancer types compared by gene and sex (univariate comparison). Table 2 gives information about mean ages at diagnosis, cumulative lifetime risks at 70 years, and SIRs with regard to the general population. Table 3 summarizes the results of multivariate modeling of sex and mutated gene, adjusted for registry and year of birth.

Among the seven less common cancer types considered in our analysis, small bowel and ovarian cancer showed the earliest mean ages at diagnosis (mean, 46 years for small bowel and 44 years for ovarian cancer). Only cancers of the stomach, small bowel, and the ovaries were observed before the age of 30 years. The highest cumulative lifetime risks were observed for breast cancer (14.4%; 95% CI, 9.5% to 19.3%) and small bowel cancer in men (12.0%; 95% CI, 5.7% to 18.2%). Stomach cancer in female mutation carriers had the lowest lifetime risk (2.6%; 95% CI, 1.1% to 4.1%). Clearly significant risk differences between male and female mutations carriers could only be
Fig 1. Age-dependent cumulative risks for (A, B) gastric, (C, D) small bowel, (E, F) urinary bladder, and (G, H) other urothelial cancers, compared by sex (left panels) and by mutated gene (right panels).
observed for small bowel cancer, with a hazard ratio (HR) for male carriers of 2.52 (95% CI, 1.41 to 4.50). Male carriers had a two-fold increased risk for gastric cancer compared with women (HR = 2.00; 95% CI, 0.98 to 4.10); however, this difference was borderline nonsignificant in the multivariate analysis (P = .058). Cancers of the urinary tract showed no significant risk differences by sex in the multivariate analysis, even though the risk was estimated to be higher for male carriers.

Risk differences between MLH1, MSH2, and MSH6 mutation carriers were found for gastric and small bowel cancer, cancers of the urinary tract (urinary bladder and other urothelial cancers), ovarian cancer, and prostate cancer. For stomach and small bowel cancer, MLH1 and MSH2 mutation carriers had similar cumulative risks; however, MSH6 carriers showed a significantly decreased risk compared with MLH1 carriers. Regarding urothelial cancer, MSH2 mutation carriers had a considerably higher risk compared with MLH1 and MSH6 mutation carriers. A similar gene-dependent risk pattern was found for prostate cancer, although quantitative risk estimation was not possible in the multivariate analysis. A different pattern was found for ovarian cancer, with comparable risks between MSH2 and MSH6 mutation carriers and a reduced risk for MLH1 mutation carriers.

All seven cancer types were significantly more frequent and occurred earlier than expected in the general population (Table 2). This was even the case for breast cancer, with an SIR of 1.9 (95% CI, 1.4 to 2.4) and a mean age at diagnosis of 52 years (range, 30 to 76 years). The highest SIRs were found for small bowel cancer and urothelial cancer (SIRs between 100 and 251). There was no significant heterogeneity in cancer risks between the German and Dutch sample except for stomach cancer, for which the risk was significantly lower in the Dutch sample (HR = 0.24; 95% CI, 0.08 to 0.67; P = .007).

### Table 2. Mean Ages at Diagnosis, Cumulative Lifetime Risks, and SIRs Compared With the General Population

<table>
<thead>
<tr>
<th>Organ</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>%</td>
<td>95% CI %</td>
</tr>
<tr>
<td>Stomach</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Range</td>
<td>28-78</td>
<td>46</td>
</tr>
<tr>
<td>Small bowel</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Range</td>
<td>25-73</td>
<td>46</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Range</td>
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<td>43-74</td>
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<td>57</td>
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<tr>
<td>Range</td>
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<td>41-74</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
<td>52</td>
</tr>
<tr>
<td>Range</td>
<td>—</td>
<td>30-76</td>
</tr>
<tr>
<td>Ovary</td>
<td>—</td>
<td>44</td>
</tr>
<tr>
<td>Range</td>
<td>—</td>
<td>26-58</td>
</tr>
<tr>
<td>Prostate</td>
<td>59</td>
<td>50-74</td>
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<tr>
<td>Age at 70 years</td>
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</tr>
<tr>
<td>Stomach</td>
<td>6.7</td>
<td>1.1 to 4.1</td>
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<tr>
<td>Small bowel</td>
<td>12.0</td>
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<td>Breast</td>
<td>—</td>
<td>9.5 to 19.3</td>
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<td>Ovary</td>
<td>—</td>
<td>5.8 to 10.3</td>
</tr>
<tr>
<td>Prostate</td>
<td>9.1</td>
<td>4.4 to 13.8</td>
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</table>

**Abbreviation:** SIR, standardized incidence ratio.

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Fig 2. Age-dependent cumulative risks for (A) breast, (B) ovarian and (C) prostate cancer, compared by mutated gene.
the analysis does not account for ascertainment bias. Further-
risks for these cancers are likely to be largely overestimated if
cancers in their families. Therefore, in retrospective studies, the
preferentially ascertained on the basis of the presence of these
cancer were not included in this analysis because patients were
MLH1 (, and
ested in describing risk differences by sex and mutated MMR gene
common cancers in patients with LS. We were particularly inter-

<table>
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<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
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<td>Male sex</td>
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<td>0.98 to 4.10</td>
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<td>MSH2</td>
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<tr>
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<td>*</td>
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<tr>
<td>Small bowel</td>
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<td></td>
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<tr>
<td>Male sex</td>
<td>2.52</td>
<td>1.41 to 4.50</td>
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<td>Male sex</td>
<td>1.73</td>
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<td>0.85 to 2.78</td>
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<td>MSH2</td>
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<td>MSH6</td>
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<td>MSH2</td>
<td>0.92</td>
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<tr>
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<td>MSH2</td>
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<td>MSH6</td>
<td>2.59</td>
<td>1.11 to 6.05</td>
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</tr>
<tr>
<td>MSH6</td>
<td>*</td>
<td>*</td>
<td>*</td>
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</table>

NOTE. Female sex and MLH1 gene were reference categories adjusted for registry (Germany / Netherlands) and year of birth.
Abbreviation: MMR, mismatch repair.

aNo estimation possible.

DISCUSSION

In this retrospective cohort study, we investigated the risks of less common cancers in patients with LS. We were particularly interested in describing risk differences by sex and mutated MMR gene (MLH1, MSH2, and MSH6). Colorectal cancer and endometrial cancer were not included in this analysis because patients were preferentially ascertained on the basis of the presence of these cancers in their families. Therefore, in retrospective studies, the risks for these cancers are likely to be largely overestimated if the analysis does not account for ascertainment bias. Furthermore, we restricted our analysis to individuals with a proven mutation. Many other studies have also included family members with unknown mutation status. These members were assumed to have a mutation if they already had been diagnosed with colorectal or endometrial cancer (so-called probable mutation carriers). However, it cannot be excluded that some of these individuals had only sporadic cancer. Consequently, the inclusion of such individuals into the analysis may lead on the one hand to an underestimation of less common cancer risks and on the other hand to an overestimation of colorectal and endometrial cancer risks.

Gastric cancer risk was significantly increased compared with that of the general population (SIR 9.8 for male and 7.2 for female mutation carriers). We also found that gastric cancer risk was considerably lower in the Dutch than in the German study cohort (HR = 0.24). This explains why a separate Dutch study reports only SIRs of 3.8 for male and 2.7 for female individuals. However, the reason for this risk difference remains unclear, especially because age-standardized incidence rates are not largely different between the German and Dutch general population. Aarnio et al reported an SIR of 6.9 in 360 proven and obligate mutation carriers, which is in agreement with our present finding. The cumulative lifetime risks for gastric cancer in MLH1 and MSH2 carriers in our study were also in concordance with the figures reported by Watson et al. Also in agreement with the study by Watson et al, we did not detect a significant risk difference for gastric cancer between MLH1 and MSH2 mutation carriers. In contrast to the study of Watson et al, we found a relevant difference in gastric cancer risk between male and female individuals (HR = 2.00), which was significant in the univariate analysis and nearly significant in the multivariate analysis (P = .02 and P = .058, respectively). Barrow et al also report significant differences between male and female patients.

Small bowel cancer showed the highest risk increase compared with the general population (SIR of 251 for male and 112 for female mutation carriers). Cumulative risk figures at age 70 years are higher than reported by others. Male carriers had a significantly higher risk than female carriers (HR = 2.5). Small bowel cancer risk was significantly lower in MSH6 mutation carriers compared with MLH1 and MSH2 mutation carriers.

Bladder cancer was significantly more frequent than expected in the general population (SIR of 8.5 for male and 16.2 for female mutation carriers). MSH2 mutation carriers had a considerably increased risk to develop bladder cancer compared with MLH1 and MSH6 carriers. This is in accordance with two other studies, which also found significantly higher risks in MSH2 mutation carriers. Our result supports the observation that bladder cancer is part of the tumor spectrum of LS.

The risk for ovarian cancer was approximately 14 times higher than in the general population, which is consistent with data from Aarnio et al. Interestingly, MSH2 and MSH6 carriers had significantly higher risks than MLH1 carriers (HR = 2.1 for MSH2 and 2.6 for MSH6, respectively). Watson et al have reported previously substantially higher risks for carriers of MSH2 mutations than for MLH1-mutation carriers.

Our analysis suggests that breast cancer risk is significantly elevated compared with the general population (SIR of 1.9). There was no significant heterogeneity for breast cancer risk between the German and the Dutch registry. There were also no differences in the risks between MLH1, MSH2, and MSH6. Most other studies did not show a significantly higher risk for breast cancer. However, Scott et al reported a significant overrepresentation of breast cancers in MSH2 mutation carriers (SIR = 14.77). The lifetime risk for breast cancer was approximately 14% in our analysis, which is considerably higher than reported in the study by Watson et al (5.4%). In the light of these conflicting results regarding breast cancer risks, larger studies are required to further investigate whether breast cancer is part of the tumor spectrum of LS.
The risk of prostate cancer was significantly increased compared with that of the general population (SIR of 2.5). The highest risk was found in carriers of MSH2 mutations. Grindedal et al recently reported an even higher risk increase for prostate cancer (SIR of 5.9) in 106 mutation carriers. They reported that prostate cancer was only observed in carriers of MSH2, MSH6, and PMS2 mutations but not in those with MLH1 mutations.

Pancreatic cancer and other types of cancer could not be included in our analysis because the number of events was too small to yield conclusive risk estimates. However, other studies suggest that the risk of pancreatic cancer is increased in families with LS compared with the general population.4

In our study, male patients with LS generally had higher risks for gastric, small bowel, and urothelial cancer than female patients. These risk differences might be explained at least in part by different environmental exposures or lifestyles (eg, regarding smoking habits, alcohol consumption, or dietary factors).24 Recently, studies have been published demonstrating an association between smoking or body mass index and colorectal adenoma or cancer risk.25-28 However, studies addressing the possible association between these factors and the less common cancers in LS are not yet available.

Our study confirms that less common cancers show organ-specific risk differences with regard to the mutated MMR gene. The reason for this gene and organ specificity is yet not well understood. The MMR system consists of different MMR proteins interacting with each other to detect and to repair DNA mismatches. It has been proposed that likely several distinct mechanisms contribute to the observed of tissue specificity (eg, cell type-specific mutator targets, specific apoptotic pathways, interactions between the MMR system and environmental factors, and others).28

Some limitations of our study should be addressed. PMS2 mutation carriers were not included in this study, because their number was far too small to obtain reasonable risk estimates. Another limitation is that retrospective analyses may lead to an overestimation of risks for those types of cancer, which were the basis for selection (ascertainment bias).21 However, most families were identified by clustering or early onset of colorectal or endometrial cancer. Therefore, we believe that risk estimates for the less common noncolonic nonendometrial cancers should not be severely affected. However, the risk estimates from our study may not apply to mutation carriers who were ascertained under different conditions and should therefore be interpreted with caution. To overcome the specific problem of ascertainment bias, data from prospective studies are required. Ideally, to accumulate sufficient data in an acceptable time frame, this problem should be tackled in international collaborative efforts combining data from large national registries. Until results from prospective studies become available, retrospective analyses must be considered as the best available basis for clinical decision making.

In summary, there is increasing evidence in the literature that the risks of less common cancers in LS depend on sex and the specific mutated MMR gene. These two factors should be taken into account for specific cancer surveillance strategies. For instance, MSH2 mutation carriers may be included in specific surveillance for urothelial and prostate cancer. In Germany, annual upper GI endoscopy is currently recommended for all patients with LS irrespective of the affected MMR gene. However, this advice could possibly be restricted to patients with MLH1 or MSH2 mutations, as the risk for gastric or small bowel cancer is considerably lower in patients with MSH6 mutations.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) and/or an immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which a reasonable person might consider a different level of disclosure.

**Employment or Leadership Position:** Hans K. Schackert, GWT of TU Dresden (C); Heike Goergens, GWT of TU Dresden (C) Consultant or Advisory Role: Hans K. Schackert, Medical Care Unit GmbH of the University Hospital Dresden (C); Heike Goergens, Medical Care Unit of the University Hospital Dresden (C); Wolff Schmiegel, Roche (C), AstraZeneca (C); Gabriela Moeslein, Bayer HealthCare Pharmaceuticals (C) Stock Ownership: None Honoraria: Hans K. Schackert, onkovis GmbH, Merck Pharma GmbH (C); Heike Goergens, onkovis GmbH, Merck Pharma GmbH; Wolff Schmiegel, Merck, Roche, Abbott Laboratories, AstraZeneca Research Funding: Wolff Schmiegel, Roche, sanofi-aventis, Pfizer Expert Testimony: None Other Remuneration: Wolff Schmiegel, Roche, Merck, AstraZeneca

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Data analysis and interpretation: Christoph Engel, Markus Loeffler, Wolff Schmiegel, Tom G.W. Letteboer, Fred H. Menko, Hans F.A. Vesen

Manuscript writing: All authors

Final approval of manuscript: All authors

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Although all authors completed the disclosure declaration, the following author(s) and/or an immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which a reasonable person might consider a different level of disclosure.

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