

# Reduced life expectancy seen in hereditary diseases which predispose to early-onset tumors

D Gareth R Evans<sup>1</sup>  
Sarah Louise Ingham<sup>2</sup>

<sup>1</sup>Genetic Medicine, Manchester Academic Health Science Centre, Central Manchester Foundation Trust, St Mary's Hospital, Manchester, UK; <sup>2</sup>Centre for Health Informatics, Institute of Population Health, The University of Manchester, Manchester, UK

**Abstract:** There are several hereditary diseases that are a predisposition to early-onset tumors. These include syndromic conditions like neurofibromatosis 1 and 2, von Hippel–Lindau syndrome, Gorlin syndrome, multiple endocrine neoplasia, and familial adenomatous polyposis; and conditions which are usually not possible to diagnose clinically in a single individual, such as Lynch syndrome and *BRCA1/2*. Understanding of the mortality in hereditary cancer predisposing diseases is important for developing effective disease treatment programs. A number of studies have been undertaken to investigate the genetic predictors, prevalence and incidence, and treatment outcomes of these diseases; however, the majority examine only the most common of these diseases (eg, neurofibromatosis or *BRCA*), or look into postoperative survival. The mortality of individuals who are diagnosed with one of these hereditary diseases remains an area for investigation. This review is the first to attempt identification of studies investigating life expectancy in hereditary diseases which predispose to early-onset tumors.

**Keywords:** mortality, survival, life expectancy, early-onset, tumors

## Introduction

Contemporary studies have shown the hereditary diseases of neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), familial adenomatous polyposis (FAP), von Hippel–Lindau syndrome (VHL), Gorlin syndrome (GS), and Lynch syndrome (LS) to be major causes of early-onset tumors in adults, often leading to reduced life expectancy and a greater dependence on health services.<sup>1,2</sup>

At a population level, these hereditary diseases are rare; however, in those diagnosed, they can have dramatic consequences with regards to quality of life and mortality.<sup>1</sup> To date, a number of studies have examined the impact of these diseases (mainly focusing on the most common of these conditions [eg, neurofibromatosis]) and postsurgical survival.<sup>1–5</sup> The number of studies which investigate the full effect of hereditary diseases that predispose to early-onset tumors upon life expectancy remains limited.

The purpose of this review is to summarize the current knowledge within the published literature regarding hereditary cancer predisposing diseases. This information is essential for etiological research and for assessment of existing treatments. Such information aids the development of guidelines, like those produced by the National Health Institute of Clinical Excellence. This review is limited to the well-known autosomal dominant conditions (Table 1).

Correspondence: D Gareth R Evans  
Genetic Medicine, Manchester  
Academic Health Science Centre,  
Central Manchester Foundation Trust,  
St Mary's Hospital, Oxford Road,  
Manchester, M13 9WL, UK  
Tel +44 161 276 6206  
Fax +44 161 276 6145  
Email [gareth.evans@cmft.nhs.uk](mailto:gareth.evans@cmft.nhs.uk)

**Table I** Chromosomal location and implications of various dominant tumor predisposing conditions

Disease	Location	Tumors	Age of tumor onset	Risk	Birth incidence	Life expectancy	References
FAP	5q	Adenomas	1st year	100%	1 in 8,600	63–70 years	1,18
		Colorectal	4–7 years	99%			
NF1	17q	Neurofibroma	1st year	100%	1 in 2,600	54–72 years	2,4,5,7,11
		Glioma	1st year	12%			
NF2	22q	Schwannomas	1st year	100%	1 in 33,000	62–69 years	1,15,17
		Meningioma	1st year	60%			
		Ependymomas	1st year	20%			
VHL	3p	Hemangioblastomas	1–2 years	90%	1 in 40,000	49–53 years	1,22–24
		Renal carcinoma	20 years	70%			
MEN1	11q	Parathyroid	5 years	95%	1 in 35,000	Close to normal	30,31
		Insulinoma	5 years	95%			
		Gastrinoma	5 years	95%			
MEN2a	10q	Medullary thyroid	3 years	80%	1 in 40,000	Reduced	
		Parathyroid	3 years	80%			
		Pheochromocytoma	3 years	80%			
MEN2b	10q	Medullary thyroid	1st year	100%	1 in 1,000,000	Reduced	
		Pheochromocytoma	1st year	100%			
Gorlin syndrome	9q	Basal cell carcinoma	5 years	90%	1 in 18,000	73.4 years	1
		Medulloblastoma	1st year	5%			
Cowden	10q	Breast cancer	30 years	60%	1 in 200,000–250,000	Reduced in women	41,43,46
		Thyroid	30 years	40%			
PJS	19p	GI malignancy	20 years	60%	1 in 25,000	58 years	33,34
		Breast/cervix	20 years	40%			
JPS	18q, 10q	GI malignancy	20 years	40%	1 in 100,000	Reduced	37,40
LFS	17p	Sarcoma	1st year	80%	1 in 30,000	Severely reduced	47,49,75
		Breast cancer (women)	16 years	95%			
		Gliomas	1st year	20%			
HDGC	16q	Gastric	<40 years	70%–80%	Very rare	Reduced	55,57,60,61
		Breast (women)	>50 years	20%–40%			
Lynch syndrome	2p, 3p, 2q, 7p	Colorectal	>16 years	50%–80%	1 in 1,000–4,000	Reduced	50–54
		Endometrium	>20 years	60%			
		Ovary/ureter	>20 years	10%			
		Gastric	>20 years	10%			
		Pancreas	>30 years	5%			
BRCA1	17q	Breast/ovary (women)	>16 years	60%–90%	1 in 1000	62 years	
BRCA2	13q	Breast/ovary (women)	>16 years	40%–90%	1 in 800	68 years	66
		Prostate	>30 years	20%			
		Pancreas	>30 years	5%			

**Abbreviations:** FAP, familial adenomatous polyposis; NF, neurofibromatosis; VHL, von Hippel–Lindau syndrome; MEN, multiple endocrine neoplasia; PJS, Peutz–Jeghers syndrome; JPS, juvenile polyposis syndrome; LFS, Li–Fraumeni syndrome; HDGC, hereditary diffuse gastric cancer; GI, gastrointestinal.

## Types of studies

There are generally two types of study assessing mortality in tumor predisposing syndromes. The first assesses survival in cohorts of ascertained patients. The second assesses mortality based on death certificate notification. The latter relies on the notification of the syndrome on the death certificate, which could only reliably occur in conditions that are easily diagnosed in a single individual. NF1 can be identified easily by cutaneous examination and documentation of café au lait patches and neurofibromas; NF2 by the

presence of bilateral vestibular schwannomas; and FAP by the presence of >100 adenomas. However, this would not be possible in either LS or *BRCA1/2*. We used the following search terms to identify the articles required for this review: mortality, survival, and life expectancy by each of the conditions studied.

## Neurofibromatosis (type 1)

The neurofibromatoses are the most well-documented of the cancer predisposing hereditary diseases and can

be divided into three genetic types: NF1, NF2, and schwannomatosis. NF1 is an autosomal dominant disease caused by mutations in the NF1 gene at 17q11.2 on chromosome 17 that normally codes for the cytoplasmic protein neurofibromin.<sup>3,4</sup> The pathogenic mutations lead to a wide variety of symptomatic presentations, though the distinctive phenotypic expressions include >6 café au lait patches, >2 Lisch nodules of the iris, as well as central nervous system tumors, and vasculopathy.<sup>4-7</sup> The overwhelming characteristic feature of NF1 is peripheral nerve sheath tumors (neurofibromas, malignant peripheral nerve sheath tumors [MPNST]), which form as a result of the loss of the tumor suppressor protein neurofibromin.<sup>3-6</sup> MPNST are a major cause of reduced life expectancy in NF1 patients.<sup>5,7,8</sup>

Epidemiological data shows NF1 to be a relatively common autosomal dominant disease with birth incidence estimates ranging from 1 in 2,500 to 1 in 3,000 live births.<sup>5,7,9</sup> Evans et al conducted a study looking into the prevalence and incidence of tumor-prone syndromes in North West England and found an estimated birth incidence for NF1 of 1 in 2,712, based on the highest incidence decade values.<sup>10</sup>

A number of studies have looked at the genetic and phenotypic expression of NF1; however, relatively few have looked into the effect on mortality. Recently reported estimates of reduced life expectancy vary from 8 years to 15 years.<sup>1,2,7</sup> An Italian death certificate study by Masocco et al reported a dramatic increase in mortality between adolescence and 40 years, with a further increase after 50 years of age.<sup>5</sup> They also found a mean reduction in life expectancy of 20 years in comparison to the general population.<sup>5</sup> Another death certificate study in the United States assessed cause of death in 3,770 NF1 patients, who died between 1983–1997, and found a reduced life expectancy of 15.7 years (95% confidence interval [CI] 15.0–16.3) compared to the general population.<sup>7</sup> Mean age at death was recorded as 54.4 years in NF1 patients and 70.1 years in the general US population.<sup>7</sup>

A 12-year follow-up study conducted by Zöller et al on 70 Swedish NF1 adults looked into life expectancy, mortality, and cause of death.<sup>11</sup> Compared to the general Swedish population, the mean age of death (61.6 years) was 15 years younger. Compared to the 5.1 deaths expected in the general population, 22 deaths were found to have occurred in the NF1 group ( $P < 0.001$ ).<sup>11</sup> A Danish nationwide cohort of 212 NF1 patients were followed by Sørensen et al over a period of 42 years.<sup>12</sup> As with all of

the subsequent studies, Sørensen et al found significantly reduced survival rates in both those diagnosed with neurofibromatosis and their relatives compared to the general population.<sup>12</sup>

Two more recent cohort studies have again confirmed reduced life expectancy in patients with NF1. A population based study in the UK showed an 8-year reduction in life expectancy, mainly due to deaths from MPNST and glioma, although there was an increased PMR (proportionate mortality rate) from cardiovascular disease in men (relative risk 4.2; 95% CI 2.6–6.2).<sup>2</sup> The other recent cohort study was from France;<sup>4</sup> consecutive NF1 patients referred to the National French Referral Center for neurofibromatosis were included.<sup>4</sup> Between 1980 and 2006, 1,895 NF1 patients were followed up for a median of 6.8 years (range, 0.4–20.6 years). Vital status was available for 1,226 (65%) patients, of whom 1,159 (94.5%) survived and 67 (5.5%) died. Overall mortality was significantly increased in the NF1 cohort (PMR, 2.02; CI, 1.6–2.6;  $P < 10^{-4}$ ). The excess mortality occurred among patients aged 10–20 years (PMR, 5.2; CI, 2.6–9.3;  $P < 10^{-4}$ ), and 20–40 years (PMR, 4.1; 2.8–5.8;  $P < 10^{-4}$ ).<sup>4</sup> Significant excess mortality was found in both males and females. In the 10–20 year age group, females had a significant increase in mortality compared to males (PMR, 12.6; CI, 5.7–23.9; and PMR, 1.8; CI, 0.2–6.4, respectively). The cause of death was reported for 58 (86.6%) patients; MPNST was the most frequent cause of death (60%). They found significantly increased PMRs, indicating excess mortality in NF1 patients compared to the general population. Overall mortality was significantly increased in NF1 patients aged 10–40 years and tended to be higher in females than in males. There was no excess mortality >40 years of age, which may have been due to limited numbers in the older age groups.<sup>4</sup>

Cohort studies may be biased by ascertaining more severely affected cases, although this would be ameliorated by a highly ascertained cohort.<sup>2</sup> Although death certificate studies might be expected to overcome the ascertainment bias of cohort studies, they are dependent on NF1 being accurately recorded on the death certificate. In the Evans et al 2011 study, only 35% of NF1 patients with available death certification had NF1 as a contributing cause on the death certificate.<sup>2</sup> The use of death certificates by Rasmussen et al in 2001<sup>7</sup> and Masocco et al in 2011,<sup>5</sup> therefore, needs to be assessed against the likelihood that all deaths associated with NF1 were recorded. The Rasmussen et al study found that NF1 was only recorded

on 1 in 8,679 deaths.<sup>7</sup> In the Masocco et al study, this was even lower at 1 in 10,685.<sup>5</sup>

In summary, while there are clearly excess deaths from malignancy in NF1 in the first 40–50 years of life and overall life expectancy is reduced, it is likely that life expectancy overall is not reduced by the 15–20 years suggested in many studies.

## Neurofibromatosis (type 2)

NF2 is a chronic autosomal dominant disease, which is genotypically expressed by the inactivation of the NF2 tumor suppressor gene on chromosome 22q12.<sup>13,14</sup> Phenotypic expression of this genotypic loss includes spinal tumors, peripheral nerve tumors, and brain tumors, with vestibular schwannomas being the hallmark manifestation.<sup>14,15</sup> Indeed, an evaluation study into the predictors of risk by Mautner et al revealed almost 95% of individuals diagnosed with NF2 presented vestibular schwannomas, with 90% presenting with spinal tumors.<sup>16</sup> Upon examination, the mortality rate of NF2 can be related to the development of these benign tumors, which can develop in uncontrolled numbers, with (until recently) surgery and sometimes radiotherapy the only effective treatments.

With an incidence of 1 in 33,000,<sup>13</sup> NF2 is a rare disease affecting only a small number of the general population. Despite its uncommon occurrence, NF2 is a chronic condition that substantially reduces life expectancy in those reported as sufferers.<sup>15</sup> However, as with NF1, although life expectancy is shortened in comparison to the general population, improvement in treatments shows mean actuarial survival to be 62 years.<sup>17</sup> Conversely, this same study by Evans et al looked into symptoms and survival in 150 NF2 patients and found a mean age of death of 36.25 years for 40 cases, highlighting the presence of intra- and inter-family differences in disease presentation.<sup>17</sup> Advancements in surgical and pharmacological treatments continue to improve life expectancy in those diagnosed with NF2. A more recent assessment of NF2 mortality in a population-based sample showed a life expectancy of 69 years, with an improvement of 14.7 years since the inception of a genetic register in 1990.<sup>1</sup> Predictors of mortality include mutation type (truncation is worst), and the presence of meningiomas; importantly, treatment in a specialist center was associated with improved mortality.<sup>15</sup>

## Familial adenomatous polyposis

FAP is an autosomal dominant disease caused by mutations in the *APC* gene on chromosome 5q. Characteristics include a predisposition to benign and malignant colorectal and

duodenal tumors, as well as rare malignant brain tumors, thyroid cancer, and hepatoblastoma.<sup>1</sup> If unscreened, >95% of FAP patients will develop colorectal cancer, which is therefore the main recorded cause of death.<sup>1,18,19</sup> Deaths may also occur due to duodenal cancer and infiltrative desmoid disease. Reduced life expectancy can be seen in FAP-affected individuals, with current estimates from the UK of 70.4 years.<sup>1</sup> However, life expectancy has improved dramatically by regular screening and surgical intervention to remove the at-risk colon and rectum.<sup>1,18–21</sup> Under these assumptions, current life expectancy appears to be similar to those diagnosed with NF1.<sup>1</sup>

## von Hippel–Lindau syndrome

Three studies have reported survival for patients with VHL, with two studies classifying the average survival as less than 50 years,<sup>22,23</sup> and median survival measured as 49 years.<sup>24</sup> In comparison to the other hereditary diseases that predispose to early-onset tumors, VHL is found to have the lowest life expectancy.<sup>1</sup> Survival can often be limited in patients with this disease by the development of benign tumors in highly vascular areas, such as hemangioblastomas of the central nervous system.<sup>24,25</sup> It is thought that the recurrence and number of tumors that develop within these vascular areas lead to the early death of VHL patients.<sup>22–25</sup>

## Gorlin syndrome

GS is considered to have the highest life expectancy from among the tumor predisposing syndromes.<sup>1,26,27</sup> Although the numbers of patients are small, with an estimated birth incidence of 1 in 18,000, GS is one of the more common hereditary early-onset tumor diseases.<sup>26,28</sup> In a 2011 study, Wilding et al demonstrated a reduced life expectancy of 73.4 years.<sup>1</sup> Only 19% of deaths appeared to be related to GS, a much lower percentage than for the four conditions described above (55%–73%).<sup>1</sup> We were unable to find any other papers assessing life expectancy. A potential reason for the relatively normal life expectancy in GS patients could be that the main complications of multiple basal cell carcinomas and benign jaw cysts only rarely metastasize, and even medulloblastomas in GS have relatively high survival rates.<sup>26,28</sup>

## Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN) encompasses several distinct syndromes (Table 1) featuring tumors of endocrine glands, each with its own characteristic pattern. In MEN1, the tumors are predominantly benign, while in MEN2, tumors are often malignant, with medullary thyroid cancer being the

main problem.<sup>29</sup> A study assessing mortality in MEN1 found that 17/60 (28%) individuals died of MEN1-related causes, most commonly metastatic islet cell tumors (ten patients). The remaining patients died of causes unrelated to MEN1. The overall 20-year survival of MEN1 patients in this series was 64% (95% CI 56%–72%) and that of an age- and gender-matched population was 81% ( $P < 0.001$ ). This suggested an increased risk of premature death in MEN1.<sup>29</sup> However, a population based study in Finland showed that over a 30-year period the spouses of MEN1-affected individuals lived the same length of time.<sup>30</sup>

While the life expectancy in MEN1 may not be dramatically affected, this may not be the case in MEN2, particularly for those born with de novo MEN2b mutations that can cause medullary thyroid cancers in the first 5 years of life. There is nonetheless very little information regarding life expectancy in MEN2 in the literature. One 20-year follow-up study showed 10-year survival of only 68% in medullary thyroid cancer patients.<sup>31</sup> However, the identification of the *RET* oncogene as the cause of MEN2a and MEN2b and early thyroidectomy before cancer diagnosis almost certainly normalizes life expectancy.<sup>32</sup>

## Peutz–Jeghers syndrome

Peutz–Jeghers syndrome (PJS) is characterized by a typical benign polyp that can occur throughout the gastrointestinal tract and mucocutaneous pigmentation. The majority of patients that meet the clinical diagnostic criteria have a causative mutation in the *STK11* gene at 19p13.3;<sup>33</sup> however, it is the high risk of gastrointestinal malignancy, as well as breast and a rare form of cervical cancer that can affect life expectancy. Among 72 patients with PJS at St Mark's Hospital (London, UK), malignant tumors developed in 16 (22%), causing death in all but one.<sup>33</sup> There were nine gastrointestinal and seven nongastrointestinal tumors. The relative risks of death from gastrointestinal cancer and all cancers were 13 (95% CI 2.7–38.1) and 9 (95% CI 4.2–17.3), respectively. The chance of dying of cancer by the age of 57 was 48%.<sup>33</sup>

In a more recent study of 133 PJS patients, 49 cancers were diagnosed in 42 patients (32%) in 5,004 person-years of follow-up, including 25 gastrointestinal cancers. The median age at first cancer diagnosis was 45 years.<sup>34</sup> The cumulative cancer risk was 20% at age 40, increasing to 76% at age 70. Cumulative cancer risks were higher for females than for males, reflecting the malignancies of breast and cervix ( $P = 0.005$ ).<sup>34</sup> The relative cancer risk was higher in PJS patients than in the general population (hazard ratio [HR] 8.96; 95% CI 6.46–12.42) and higher among female

(HR 20.40; 95% CI 13.43–30.99) than among male patients (HR 4.76; 95% CI 2.82–8.04). Forty-two patients died at a median age of 45 years, including 28 cancer-related deaths (67%).<sup>34</sup> Mortality was increased in this Dutch cohort compared to the general Dutch population (HR 3.50; 95% CI 2.57–4.75).<sup>34</sup>

## Juvenile polyposis syndrome

First defined in 1964 by McColl<sup>35</sup> and followed by several case reports in the late 1960s (eg, Johnston et al),<sup>36</sup> juvenile polyposis syndrome (JPS) is a familial condition that affects the upper and lower gastrointestinal tract. JPS is a relatively rare condition, affecting approximately 1 in 100,000 children.<sup>37</sup> Deletion and/or mutation is seen in the tumor-suppressor genes *SMAD4* and *BMPRIA* on the chromosomes 18q and 10q, respectively.<sup>37,38</sup> At initial presentation, symptoms include multiple polyps, mucosal lesions, rectal bleeding, diarrhea, and exudative enteropathy.<sup>37,38</sup> Such phenotypic expression, particularly in the gastrointestinal tract, greatly reduces the life expectancy of the affected children.<sup>36–39</sup> A more recent study in 2007 by Brosens et al<sup>40</sup> addressing colorectal cancer has shown a cumulative lifetime risk of 38.7% in JPS, with a mean diagnosis age of 43.9 years. We found that very few studies have looked into JPS and even fewer have reported on mortality.

## Cowden's syndrome

Cowden's syndrome is a rare familial autosomal disease that has been localized through several genetic studies to chromosome 10q23 and the tumor-suppressor gene *PTEN*.<sup>41–43</sup> The phenotypic hallmarks of this disease include multiple facial papules, trichilemmomas, oral papillomas, and macrocephaly, though there are varied expressions of the disease even among families.<sup>42,44</sup> Breast cancers are the most frequent malignancies reported to be associated with this syndrome, though various organ systems can be involved, including gastrointestinal and urogenital.<sup>41,43,44</sup>

Originally estimated as having an incidence of 1 in 1,000,000,<sup>43</sup> a more recent investigation into the novel genotype–phenotype correlations of Cowden's syndrome revised the figure by post-genetic identification to a prevalence of 1 in 200,000–250,000 within a Dutch population.<sup>41,43</sup> Further investigations have examined potential chemoprevention and treatment of Cowden's disease in mouse models, with the intent to increase life expectancy.<sup>45</sup> However, as with many of the other diseases, a large body of work can be found on the genetics of the syndrome,<sup>46</sup> though few articles discuss the mortality and life expectancy of Cowden's patients.



## Li-Fraumeni syndrome

It is likely that life expectancy is substantially reduced in Li-Fraumeni syndrome, which is an autosomal dominant disorder caused by germ-line mutations in the *TP53* gene.<sup>47–49</sup> Mutation carriers have a 20% chance of developing malignancy in childhood (particularly soft tissue and osteosarcoma, glioma, and adrenal carcinoma) and a very high chance of sarcoma and brain tumors in adulthood. Women have close to a 100% lifetime risk of malignancy, as the risk of breast cancer at <50 years is higher than that for *BRCA1/2*.<sup>47,49</sup> There have been no studies that have directly addressed life expectancy in a large series of mutation carriers, but the very early onset of malignancy and poor survival means that life expectancy is likely to be below 40 years of age on average. A recent study using multi-modal screening, including whole body MRI scans, found tumors in seven of 15 screened mutation carriers. All 15 were alive after a mean follow-up time of 47 months (compared with two of ten [20%] mutation carriers in whom 12 malignant tumors occurred but who did not undergo surveillance). Among those diagnosed with a cancer, survival was better in the surveillance group than the non-surveillance group (100% versus 21.4%,  $P < 0.001$ ).<sup>48</sup>

## Lynch syndrome

Hereditary nonpolyposis colorectal cancer, also known as Lynch syndrome (LS), is an autosomal dominant disorder with germ-line mutations in the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*.<sup>50,51</sup> After compiling information from research articles, the hallmark characteristic of LS is noted as early-onset colorectal cancer, with significant increased risk for cancers of the stomach, small intestine, upper urinary tract, uterus, ovary, and brain.<sup>50,51</sup> In reviewing research articles which studied eligible populations, we see that all of the articles report a reduction in life expectancy for those diagnosed with LS.<sup>50–54</sup> de Jong et al<sup>50</sup> studied 2,788 LS carriers and close relatives and identified 445 subjects who had died because of cancer. The three most frequent causes of cancer-related deaths were colorectal (50.3%), endometrial (6.7%), and brain tumors (6.7%). A significant decrease (70%) in SMR (standardized mortality ratio) for colorectal cancer was seen over time ( $P < 0.001$ ). A significantly increased SMR was found for cancer of the small bowel (SMR = 18.3), brain (SMR = 9.1), kidney/ureter (SMR = 5.9), ovary (SMR = 2.3), pancreas (SMR = 2.2), and stomach (SMR = 2.1). Colorectal cancer surveillance reduces the risk of cancer and improves survival in LS.<sup>53</sup> Life expectancy may also be improved by more extensive colectomy at diagnosis, with 2.3 years of extra life predicted

for a 27-year-old undergoing subtotal colectomy over hemicolectomy.<sup>54</sup> We could not identify any study that assessed overall life expectancy in LS.

## E-cadherin hereditary diffuse gastric cancer

Germ-line mutations have been identified in the *CDH1* gene found to encode the E-cadherin protein normally associated with calcium-dependent epithelial cell adhesion.<sup>55</sup> These recently identified gene mutations are symptomatically identified by diffuse gastric carcinoma, endometrial cancer, ovarian cancer, and lobular breast carcinomas.<sup>55–58</sup> Lifetime risks for these mutations (chromosome 16q) are approximately 70%–80% for gastric cancer and 40%–60% for breast carcinomas in women.<sup>59,60</sup> The prognosis of upper gastric carcinomas is poor, with only a 10% survival rate over a 5-year period, decreasing to 4% for total stomach involvement.<sup>55,57</sup> Compiling information on this rare disease has shown that around 25%–30% of hereditary diffuse gastric cancers are associated with a familial mutation in the *CDH1* gene.<sup>59,60</sup> Reduced life expectancy is assumed, as undiagnosed late-stage gastric cancer has a high mortality rate of <20% 5-year survival.<sup>60,61</sup> A cohort study assessing hereditary diffuse gastric cancer found the average age of onset for this disease to be 38 years.<sup>62</sup> The majority of previous publications have discussed the benefits of prophylactic gastrectomy rather than addressing life expectancy of individuals diagnosed with the condition.<sup>55–61</sup>

## BRCA1/2

Female *BRCA1* and *BRCA2* mutation carriers have reduced life expectancy mainly due to early death from breast and ovarian cancer.<sup>63–66</sup> Life expectancy may be worse in *BRCA1* carriers due to the greater risk of and poorer survival from ovarian cancer.<sup>66</sup> Risk-reducing surgery is predicted to improve survival amongst female carriers of pathogenic mutations in both *BRCA1* and *BRCA2*.<sup>63,6</sup> Most of this benefit is likely to occur from primary prevention of breast and ovarian cancer in women currently unaffected. However, a recent decision analysis demonstrated only a minor advantage from risk reducing mastectomy over surveillance with MRI.<sup>64</sup> Formal direct evidence for an improvement in survival in *BRCA1/2* carriers was reported for risk-reducing bilateral salpingo-oophorectomy (RRBSO),<sup>66–69</sup> and a survival advantage was also seen in women with RRBSO after diagnosis of breast cancer.<sup>70</sup> However, no formal direct evidence of a survival advantage after bilateral risk reducing mastectomy alone has yet emerged. This may be related, in part, to better survival

from breast cancer, particularly since the advent of MRI screening and the detection of small primary tumors. The greatest gains of up to 10 years in life expectancy have been predicted for carriers that undergo both bilateral risk reducing mastectomy and RRBSO soon after genetic testing.<sup>65</sup> Survival is influenced by reduction in the incidence and death from both breast and ovarian cancer.<sup>66–70</sup> There have been few long term studies addressing survival in large numbers of carriers,<sup>66,67</sup> as mutation testing and predictive genetic testing has only been widely available since the late 1990s. Six hundred and twelve *BRCA1* and 482 *BRCA2* female mutation carriers in a study in North West England were assessed for survival.<sup>66</sup> Life expectancy was significantly reduced for *BRCA1* carriers compared with *BRCA2* ( $P = 0.0002$ ). This effect was attributable to an increased death rate from ovarian cancer ( $P = 0.04$ ). Kaplan–Meier analysis revealed a better long-term survival from early-stage ovarian cancer in *BRCA2* carriers, but no significant differences in deaths from breast cancer or from women presenting with late-stage ovarian cancer. There was no other major contributing cause of death other than breast/ovarian cancer in *BRCA1/2* female carriers. Only 52.6% of female *BRCA1* mutation carriers were alive by 60 years of age compared to 68% of *BRCA2* carriers. Life expectancy in male carriers is unlikely to be substantially shortened, although male *BRCA2* carriers have an 8%–13% risk of breast cancer and up to a 25% risk of prostate cancer.<sup>71,72</sup>

## Discussion

Life expectancy is reduced across the great majority of tumor predisposing syndromes. Reduction in life expectancy is in large part due to the tumors themselves. Improvements in treatment and organization of medical services and, in particular, genetic registers is likely to have improved survival in most of these conditions, especially in the last 25 years.<sup>1</sup> Although many treatments for tumor-prone conditions are similar to those for the sporadic tumor counterparts, the beginning of personalized medicine is leading to more targeted treatment. Although not yet licensed, poly ADP ribose polymerase inhibitors offer great promise in the treatment of *BRCA1*- and *BRCA2*-related cancers. There is also evidence that such tailoring of treatment may be necessary in LS, as standard therapy with 5 fluorouracil may not be effective.<sup>73</sup> Survival may also differ between the tumors in the syndromes and their sporadic counterparts. *BRCA1/2*-related ovarian cancers appear to have better survival than expected due to greater sensitivity to platinum-based therapy. Survival is often much better in LS cancers, most notably in ovarian cancer.<sup>74</sup> Survival in Li–Fraumeni cancers, in contrast, is often very

poor.<sup>75</sup> In NF1-related tumors, survival can be better than in sporadic disease, for instance, for optic pathway tumors<sup>76</sup> or worse, as in MPNST.<sup>77</sup>

Perhaps the greatest improvement in life expectancies has come from surgical prevention. Colectomy in FAP has increased life expectancy by 15–20 years,<sup>1</sup> and extended right hemicolectomy is recommended for treatment of colorectal cancers proximal to the rectum in LS. Thyroidectomy is a vital tool for prevention in MEN2,<sup>31,32</sup> and oophorectomy is a proven way to prolong life in *BRCA1/2* mutation carriers.<sup>67</sup> Hopefully the future of personalized medicine will provide alternatives to these proven surgical options.

## Conclusion

In summary, this is an attempt to fully describe the current knowledge of reduced life expectancy in autosomal dominant diseases resulting in early-onset tumors. These results are key to the understanding and development of optimal screening, prevention, and treatment programs for the management of individuals with these hereditary diseases. All the diseases examined show general reduced life expectancy among those diagnosed, though the severity of this reduction varies greatly between the conditions. MEN1 often presents with benign tumors although slightly reduced, life expectancy within these individuals has been found to be close to the general population. In contrast, VHL and Li–Fraumeni syndrome both lead to a severe reduction in life expectancy due to the high number and location of the tumors that develop. There is evidence for improvement in life expectancy in a number of conditions with well-organized systematic screening, such as in LS and FAP.

The number of studies investigating the different hereditary early-onset tumors is large and diverse. However, only a limited number of journal articles were found to examine life expectancy in these diseases, particularly in the rarer of the germ-line mutations. The high fatality rate among these uncommon autosomal dominant diseases provides strong justification for further research into life expectancy.

## Disclosure

The authors report no conflicts of interest in this work.

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