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Attitudes About Predictive MEN1 Genetic Testing in Minors

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ATTITUDES ABOUT PREDICTIVE *MEN1* GENETIC TESTING IN MINORS

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A

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Multiple Endocrine Neoplasia type 1 (MEN1) is a hereditary cancer syndrome characterized by tumors of the endocrine system. Tumors most commonly develop in the parathyroid glands, pituitary gland, and the gastro-entero pancreatic tract. MEN1 is a highly penetrant condition and age of onset is variable. Most patients are diagnosed in early adulthood; however, rare cases of MEN1 present in early childhood. Expert consensus opinion is that predictive genetic testing should be offered at age 5 years, however there are no evidence-based studies that clearly establish that predictive genetic testing at this age would be beneficial since most symptoms do not present until later in life. This study was designed to explore attitudes about the most appropriate age for predictive genetic testing from individuals at risk of having a child with MEN1. Participants who had an *MEN1* mutation were invited to complete a survey and were asked to invite their spouses to participate as well. The survey included several validated measures designed to assess participants' attitudes about predictive testing in minors. Fifty-eight affected participants and twenty-two spouses/partners completed the survey. Most participants felt that *MEN1* genetic testing was appropriate in healthy minors. Younger age and increased knowledge of MEN1 genetics and inheritance predicted genetic testing at a younger age. Additionally, participants who saw more positive than negative general outcomes from genetic testing were more likely to favor genetic testing at younger ages. Overall, participants felt genetic testing should be offered at a younger age than

most adult onset conditions and most felt the appropriate time for testing was when a child could understand and participate in the testing process. Psychological concerns seemed to be the primary focus of participants who favored later ages for genetic testing, while medical benefits were more commonly cited for younger age. This exploratory study has implications for counseling patients whose children are at risk of developing MEN1 and illustrates issues that are important to patients and their spouses when considering testing in children.

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Multiple Endocrine Neoplasia, type 1

Multiple Endocrine Neoplasia type 1 (MEN1) is a hereditary cancer syndrome characterized by tumors of the endocrine system. The most commonly associated tumors are those of the parathyroid glands, endocrine cells of the gastro-entero-pancreatic tract and the anterior pituitary gland. A clinical diagnosis of MEN1 can be made when a patient presents with two of these three classic tumor types or one of these tumors and a family history of MEN1 [1]. The majority of MEN1 tumors are not malignant. However, damaging effects can be seen from the continuous overproduction of hormones or the size and location of tumors [2]. MEN1 is inherited in an autosomal dominant manner meaning that each child of an affected person has a 50% risk of inheriting this condition. It is a rare syndrome with an estimated prevalence of 1 in 30,000 [3]. MEN1 appears to have no predilection for any ethnic group and has been seen across many different populations. Improvements in screening and diagnostic measures have greatly improved the detection rate of MEN1-related tumors in recent years, which has resulted in more successful interventions and decreased mortality.

Parathyroid Tumors

Parathyroid tumors are the most common manifestation of MEN1 and have a lifetime prevalence of 90-99% [4] [5] [6] [7]. Both hyperplasia and adenomas can be found in the parathyroids of MEN1 patients. Often these are multiple, asymmetric tumors that may involve three or four of the parathyroid glands [1]. Parathyroid tumors create excessive secretion of parathyroid hormone (PTH) leading to elevated serum calcium levels, which is a condition known as primary hyperparathyroidism (PHPT). PHPT is the first presenting sign in 40-90% of MEN1 patients [8] [9] [10] [11]. PHPT is not uncommon in the general population and is more common in females than males when sporadic [12]. Overall, MEN1 accounts for 4-5% of

PHPT patients [13]. Distinguishing features of PHPT that are suggestive of an MEN1 diagnosis are a young age of onset, males affected with PHPT, parathyroid hyperplasia rather than an adenoma, lower parathyroid hormone levels than sporadic, more severe bone involvement, and multigland involvement [1] [12] [14]. Although tumors of the parathyroid are rarely malignant, the chronic over-expression of parathyroid hormone can have lasting and damaging effects. Most notable, extended PHPT can lead to renal stones, nephrocalcinosis and renal failure. It can also lead to skeletal problems including osteoporosis usually in the fourth decade of life [14] [15] [16].

Treatment for parathyroid tumors is somewhat controversial, although surgery is the preferred management of PHPT in MEN1 patients. Indications for a parathyroidectomy in MEN1 do not differ significantly from those with sporadic PHPT. In 1990, the NIH published a consensus statement addressing indications for surgery in patients with PHPT which included strongly elevated levels of serum calcium and resulting effects of hypercalcemia, lower creatinine clearance levels, and significantly decreased bone mass [17]. Timing of surgery has also been questioned, mainly because the long-term effects of PHPT are unknown [1] [17]. This is particularly relevant to patients with MEN1, who are diagnosed with PHPT on average 30 years younger than sporadic PHPT [1].

The overall goal of surgical intervention for parathyroid tumors in MEN1 is to reduce disease persistence and recurrence. The multigland involvement and asymmetrical presentation of parathyroid glands can make surgical intervention more complicated in patients with MEN1 and it is still debated whether a subtotal parathyroidectomy or a total parathyroidectomy with autotransplantation is more effective. A subtotal parathyroidectomy involves the removal of 3 to 3.5 parathyroid glands. A total parathyroidectomy with autotransplantation involves the removal of all four parathyroid glands and autotransplantation of parathyroid tissue elsewhere

in the body, usually to the forearm. With either surgery, there is a strong concern for hypoparathyroidism, which causes low serum calcium levels affecting the nervous system, skeletal muscles, and cardiac system [18]. In roughly half of patients, permanent hypoparathyroidism can be corrected with autotransplantation emphasizing the importance of cryopreservation with either procedure [19]. Both procedures are considered acceptable treatment options by the National Comprehensive Cancer Network guidelines [20]. Unlike other endocrine tumor conditions, such as Multiple Endocrine Neoplasia type 2, prophylactic surgery is not generally recommended.

Gastro-entero-pancreatic tumors

Gastro-entero-pancreatic tumors are the second most common tumor type in patients with MEN1 and are found in up to 80% of patients [1] [21] [22]. Unlike most other MEN1 associated tumors, gastro-enteropancreatic tumors have a high risk of malignancy, with the exception of insulinomas. These neuroendocrine tumors are the most common cause of MEN1-related death accounting for two-thirds of young deaths [23]. The most common of these tumors are gastrinomas, which make up for roughly 40% of MEN1-related neuroendocrine tumors [1]. Gastrinomas lead to elevated gastrin levels and can eventually lead to Zollinger-Ellison Syndrome (ZES), a condition that presents with gastrointestinal complications including abdominal pain, diarrhea, heartburn, weight loss and gastrointestinal bleeding [24] Twenty to twenty-five percent of all patients with Zollinger Ellison Syndrome have MEN1 [25]. Patients with MEN1 can have gastrinomas in the pancreas, but most often they originate in the duodenum [26]. Both locations carry a risk of malignancy. MEN1-related gastrinomas are usually small and multifocal making them difficult to detect radiographically [26]. About 50% of patients with a gastrinoma have already had metastasis at diagnosis [1]. Surgical intervention for gastrinomas in MEN1 patients is highly controversial. Some advocate

a nonsurgical management option usually involving the use of a proton pump inhibitor to reduce gastric acid production. Others support a more aggressive, surgical approach when the tumor reaches 3 cm to prevent further metastasis [1] [27] [28].

The second most common neuroendocrine tumor, accounting for 10-12%, is an insulinoma [1] [5]. MEN1- related insulinomas are usually benign [29]. Medical management for insulinomas is less effective than surgery and therefore, surgery is the preferred treatment. A total pancreatectomy carries a high rate of morbidity and mortality and is therefore not recommended [2] [30]. However, a distal pancreatectomy with enucleation has been shown to have a very high cure rate with a low risk of recurrent disease [31]. Tumors found in the head of the pancreas should also be treated with partial pancreatectomy [14,31]. More aggressive surgical resection is recommended for MEN1-related insulinomas due to the possibility of multiple, small insulinomas throughout the pancreas [25].

Other hormone-producing neuroendocrine tumors include glucagonoma, vasoactive intestinal peptide (VIP) and somatostatinoma. These tumors are rare but can occur in up to 5% of patients with MEN1 [1] [5] [28]. Additionally, up to 36% of patients with pancreatic endocrine tumors have a non-hormone secreting tumor that may have no clinical implications except for the size, mass-effect, and malignant potential [32].

Pituitary tumors

Tumors of the anterior pituitary affect 20 to 65% of MEN1 patients [8] [11] [15] [33]. Pituitary tumors are the first presenting manifestation in roughly 17% of MEN1 patients [8] [33]. These tumors can be either non-functioning in 11 to 38% [5] [33] [6] or hormone secreting. The most common type of MEN1-related pituitary tumor is a prolactinoma. Other hormone secreting pituitary tumors include growth-hormone-secreting (5-10%), which can

cause acromegaly, and ACTH-secreting (2-5%), which can cause Cushing's disease [1] [28] [30]. Most tumors are macroadenomas and can have severe mass effects, although most are not malignant [33]. Pituitary tumors are rarely the only MEN1-related tumor seen in a patient and, therefore, often serve as the second tumor in a clinical diagnosis [33]. An isolated pituitary tumor is not highly suggestive of MEN1 as pituitary lesions have been seen with MRI in 16% of the general population [34]. MEN1 is thought to be responsible for only 2.7% of isolated pituitary adenomas [21].

Treatment for pituitary tumors in patients with MEN1 is identical to treatment for patients with sporadic pituitary tumors. This treatment includes surgery, medical management, and/or radiation [14][28]. However, success rates do not seem to be as high in patients with MEN1 as it is in patients with sporadic tumors [33] and continued screening is recommended to avoid a recurrence [1].

Other MEN1-associated tumors

Other tumors have been associated with MEN1 less commonly than the three main tumor types. Five to ten percent of patients are diagnosed with a foregut carcinoid. Of these, bronchial and gastric carcinoids are less likely to be malignant while thymic carcinoids can be aggressive and are a major cause of mortality among MEN1 patients [4][35]. Often, a subtotal or total parathyroidectomy to treat a parathyroid tumor will include removal of the thymus to avoid potential future thymic carcinoids. Adrenocortical tumors and benign thyroid tumors may also be caused by mutations in the *MEN1* gene. Some association has been seen with renal angiomyolipoma, and leiomyomas of the esophagus [5]. Collagenomas are seen in up to 72% of patients and lipomas are seen in roughly 34% [36] [37]. Several rare skin findings have also been associated with MEN1. Multiple facial angiofibromas are seen in 20 to 88% of

patients with MEN1 [36] [37]. Given the rarity of angiofibromas in the general population, MEN1 should be a highly considered differential diagnosis in their presence.

Age of Diagnosis

MEN1 is a highly penetrant condition with 90-100% of patients exhibiting clinical manifestations by age 60 years [4] [8] [38]. A few reports of patients diagnosed before age 10 years have been published, although this is rare. These include a five-year old diagnosed with a pituitary macroadenoma [39], and two eight-year olds diagnosed with an insulinoma [40] [41]. Despite rare reports of children younger than ten being diagnosed with symptoms of MEN1, the overall penetrance is reported to be only 7% for this age group [38]. Penetrance increases to 52% by age 20 and reaches 98% by age 40 [38]. Studies investigating penetrance and age of onset have all been retrospective but have generally found the average age of diagnosis to be in early adulthood [4] [8]. Specifically, primary hyperparathyroidism was diagnosed on average by age 37 years, pituitary tumors by age 40 years, and GI endocrine tumors by age 46 years [8]. However, the wide range of ages observed for the diagnosis of each tumor type emphasizes the extreme variability in age of diagnosis. The average age of death related to MEN1 appears to be around age 50 years most commonly due to neuroendocrine tumors [8] [23]. It has been noted that there is a higher rate of diagnoses at young ages within the past decade, which is likely attributable to improved screening [35]. Males and females are affected in equal numbers, although recent data suggests a slight difference in phenotype, with men having a higher prevalence of pancreatic and thymic tumors while women have a higher prevalence of pituitary tumors. There appears to be no differences between genders in the rate of hyperparathyroidism or positive genetic tests [42].

Screening

Over the past few decades, screening methods have drastically improved resulting in earlier intervention and decreased morbidity. In 2001, an international group of clinical endocrinologists published a set of guidelines for diagnosis, treatment and screening of MEN1 [1]. Since its publication, this has been widely accepted as the consensus protocol, although additional groups have published other guidelines that only slightly differ in age and frequency of screening [30]. Because most endocrine tumors are functional, biochemical screening has proven to be an effective modality. Additionally, imaging techniques are often able to detect smaller lesions and non-functioning pituitary and pancreatic neuroendocrine tumors. In general, biochemical testing is recommended on an annual basis while imaging studies are generally recommended every 1 to 3 years or when biochemical tests are abnormal.

For parathyroid tumors, screening of calcium and parathyroid hormone levels has been recommended as early as age 8 years, although others have suggested postponing screening initiation until age 20 years, which is closer to the average age of onset for primary hyperparathyroidism [1] [30]. These levels can also be used to test post-operative success and monitor for signs of recurrent disease following surgery.

Screening for functional pancreoenteric tumors can be done by evaluating their respective biochemical markers following a fasting period. Because insulinomas have been identified in patients at a particularly young age, screening is recommended beginning at age 5, whereas screening for gastrinomas can be delayed until age 20 years [1]. Regular imaging, including computed tomography (CT) scan and magnetic resonance imaging (MRI), are recommended to detect non-functional pancreoenteric tumors which may not be found through routine biochemical screening [1] [7].

Screening for pituitary disease is recommended beginning at age 5 [1] due to a reported pituitary macroadenoma in a 5-year-old patient [39]. Laboratory tests include monitoring prolactin and insulin-like growth factor 1 (IGF-1) [1] [30]. MRI of the pituitary is recommended every 3 years, regardless of biochemical results. Screening should continue after surgical treatment due to the lower curative success rates in MEN1 patients compared with those who have sporadic pituitary disease [33].

Many of the less commonly associated tumors do not hypersecrete hormones: therefore, screening guidelines tend to focus on imaging techniques rather than biochemical analysis. The main recommendation for the detection of carcinoid tumors is a CT scan or MRI every 3 years beginning at age 20 [1].

Consensus guidelines tend to recommend screening at a younger age than the average age of onset because of a few reported MEN1 diagnoses before 10 years of age. However, several authors have suggested that these recommendations are unnecessarily aggressive. A few have stated that biochemical screening can be postponed until 15 years for pituitary tumors and 20 years for all other types of tumors, with imaging being performed every three years or only if biochemical tests are abnormal [30]. Guidelines have been difficult to establish given the debate surrounding implications of an abnormal test result. The penetrance of biochemical signs in asymptomatic patients is up to 43% by age 20 years, more than twice the penetrance of MEN1 disease in symptomatic patients [11]. Similarly, it has been suggested that the low penetrance among younger age groups may be an underestimate and that asymptomatic children may actually have non-functioning neuroendocrine tumors [43]. The nature of these tumors in particular can be difficult to predict and surgery at a young age can have its own complications.

Studies have shown that genetic testing has allowed for earlier screening and can detect biochemical changes 10 years prior to the development of disease symptoms [2]. However, timing for surgical intervention is debated and often delayed until a child begins to show symptoms regardless of prior biochemical or radiographic findings [1]. The NIH consensus statement on primary hyperparathyroidism in adults recommends medical monitoring for asymptomatic patients with biochemical evidence of primary hyperparathyroidism and has specific criteria before beginning surgical intervention [17]. Guidelines are less clear for an appropriate time for intervention in children. This has raised the question of the benefits of presymptomatic screening, which poses potential risks for increased stress and anxiety in children and their parents, before any treatment would be indicated.

Molecular Genetics of MEN1

In 1997, mutations in the *MEN1* gene on chromosome 11q13 were found to be associated with the clinical diagnostic criteria for multiple endocrine neoplasia type 1. *MEN1* is comprised of 10 exons, which code for the 610 amino acid protein, *menin* [44]. This protein has been shown to play a role in DNA replication and repair, transcriptional regulation, cell division and proliferation [3]. *MEN1* is suspected to have a tumor suppressor role that follows Knudson's "two-hit" model as the majority of tumor cells show loss of heterozygosity [45]. This theory matches an autosomal dominant inheritance whereby a germline mutation in one allele accounts for the first "hit", and the second is due to a somatic mutation that then leads to tumor initiation and growth [46].

Over 450 germline mutations have been identified in the *MEN1* gene. Most mutations are frameshift insertions or deletions (41%) followed by nonsense mutations (23%), missense mutations (20%), splice site mutations (9%), in-frame deletions and insertions (6%) and large

deletions (1%) [47]. Mutations have been found throughout the coding regions and non-coding regions and no genotype-phenotype correlations have been identified. Sequencing is commercially available and is the most effective method of genetic testing. The detection rate for an *MEN1* mutation in people who meet a clinical diagnosis of MEN1 is about 65% for patients with a non-familial presentation [48] and up to 90% in patients meeting a familial MEN1 clinical diagnosis [28]. Additionally, 4% of mutations are large deletions that can be detected using multiplex ligand-dependent probe amplification (MLPA) [49]. In the event of a negative results, an MEN1 diagnosis cannot be ruled out, particularly for patients who meet clinical diagnostic criteria [28]. Medical management for these patients is the same as those with an identified mutation. Approximately 10% of patients have a *de novo* mutation [38].

Genetic Testing in Minors

Over the past several decades, genetic testing has become more widely available for numerous genetic conditions and access to testing is improving. Genetic testing is frequently used for symptomatic patients as a diagnostic tool to confirm a suspected genetic condition. Establishing a genetic diagnosis can direct personalized medical care because it provides patients and physicians with information regarding natural history and prognosis. In oncology, genetic testing has been used for many cancer syndromes to provide information regarding risks for second primary cancers or responses to various treatments. For symptomatic individuals, this diagnostic advancement has clearly demonstrated benefits in helping to diagnose and understand disease.

Genetic testing can also serve as a powerful predictive tool for the asymptomatic individual. Many hereditary cancer syndromes have prophylactic treatment options or increased surveillance methods. For many conditions, predictive genetic testing can also help

individuals anticipate and psychologically plan for a medical condition they may someday face. However, there are potential psychological risks associated with predictive testing in an asymptomatic individual; therefore, the appropriate age for predictive genetic testing for adult onset conditions is typically considered as the age of consent, and testing in minors is highly debated.

Professional Guidelines

Conditions for which genetic testing is available can be divided into three main groups with regards to the impact on minors: conditions for which there is an immediate medical benefit, conditions for which any medical benefit would be delayed until adulthood, and conditions where there is no known medical intervention that would affect disease severity. Several professional organizations have issued position statements regarding genetic testing in minors. In 1995, the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) issued a joint position statement acknowledging the importance of balancing medical and psychological benefits, family structure, and the decision-making capabilities of the minor [50]. The statement asserts that genetic testing in minors is justified when an immediate medical or considerable psychological benefit exists. When medical and psychosocial benefits would be deferred until adulthood, genetic testing should also be deferred until the patient is no longer considered a minor. For conditions in which the benefits and harms are unclear, decisions about genetic testing should be left up to the family and competent adolescents.

The American Medical Association (AMA) issued a similar set of recommendations in 1995 adding that genetic testing should be encouraged, if not required, if therapeutic measures are available [51]. The recommendations also noted the importance of making parents aware of genetic testing for adult onset conditions so they may inform their children of its availability.

The recommendations considered the possibility of testing for the benefit of other family members, and indicate that such testing should only be undertaken if not doing so would provide considerable harm to the at-risk family member.

Clinical manifestations of MEN1 are complex and thus interpretation of general testing guidelines for minors is not as straightforward compared with other syndromes. Most persons with MEN1 are not diagnosed with a syndrome-related tumor until young adulthood. Although some persons will begin to show signs of hyperparathyroidism in adolescence, surgical intervention may not necessarily take place during childhood. For most patients with MEN1, it is unclear if there is a direct medical benefit to testing before adulthood. However, rare reports exist of clinically diagnosed MEN1 in patients under the age of ten, suggesting that there may be a rare medical benefit [39] [41]. For this reason, most guidelines suggest beginning screening at age 5. However, these guidelines rarely take into account any potential psychological sequelae for both children and parents associated with frequent screening at a young age for a condition that often does not present until later in life.

Given the potential for a significant psychological impact of predictive testing on healthy minors, several authors have looked at the potential effects on minors and their families. Childhood and adolescence are marked by changing opinions and developing thought processes. As they are growing, children begin to form an individualized image that can be greatly shaped by outside events in their lives. It has been suggested that results of predictive genetic testing in minors, particularly positive results, may interfere with development of a self-concept and cause children to identify themselves by the disease they have inherited but are not yet exhibiting [52]. Particularly at young ages, many children may perceive disease and illness as a sort of punishment [53] which may influence their developing self-image. On the other hand, it has been suggested that providing genetic risk information to children at a young age could facilitate children's adjustment to their carrier status earlier as opposed to the jarring

experience of learning it later in life and perhaps not being given the opportunity to incorporate this information into their life plans [54].

As children continue to develop their self-image and self-concept, predictive genetic testing may potentially impact not only the child but also family and sibling relationships. Stigmatization is an important consideration for persons who receive mutation positive predictive genetic testing results. Examples include lowered expectations of mutation positive persons within a family or feelings of unworthiness [53]. Children who have inherited a genetic mutation associated with a hereditary condition may be impacted as parents struggle with ways to express their own guilt about having passed on this genetic condition. Additionally, several authors have pointed to the idea of "vulnerable child syndrome," where parents are overprotective of children who they perceive to be at risk of an early death because of an illness or previous close call [53] [55] [56]. Sibling relationships also may be strained when a child tests positive for a genetic condition, particularly if the other child tested negative. This can occasionally lead to feelings of survivor's guilt in the unaffected child [53].

A commonly cited reason for genetic testing in minors is to reduce the anxiety of the parents who perceive that the burden of uncertainty is greater than the knowledge of what lies ahead. However, justifying predictive genetic testing for adult onset conditions in asymptomatic children for the benefit of the parents may be viewed as a direct challenge to the child's autonomy [52]. In most legal systems, parents have the right to make medical decisions for their children until they reach the age of legal adulthood (usually 18 years) or until the child has become an emancipated minor. However, it has been advocated that most children may be able to understand, to some degree, the implications of their medical care and as such, should have an adequate say in the type of medical treatment they receive [53] [57]. Therefore, there is often a requirement to have a child assent to a procedure or test before they

have acquired the ability to fully consent [53]. This often begins when children reach age 7 while acknowledging that children have varying rates of development and maturity [50] [53]. It is assumed that a child competent of assenting is capable of understanding a medical procedure and is able to agree or disagree with a parent's decision. The principles of informed consent takes this understanding a step further whereby an individual is not only able to explain the procedure and testing that will take place, but also exhibits a voluntary desire to have the testing, a clear understanding of the risks, benefits, and alternative options, and recognition of the direct and indirect impacts a test can have on the individual, family members or others [52] [53]. It is difficult to state at what age a person is capable of providing adequate informed consent given the differing rates of maturity. However, in most legal systems the age of 18 has been established as a point at which most individuals can make comprehensive decisions about their own health, medical care, and personal rights.

Upholding a child's future autonomy is important in maintaining their ability to make independent decisions for their own life plan and health care management. Genetic testing affords the ability to predict an outcome that previously would have been left unknown until the development of disease. But with advances in genetics, patients have had to balance their rights to know their medical future with their rights not to know what lies ahead [57]. In fact, since the discovery of the *HD* gene responsible for Huntington disease, the uptake of genetic testing has only been between 5-20% [58]; albeit there are no medical interventions available to reduce the burden of Huntington disease. Among the most commonly cited reasons for declining genetic testing for Huntington disease has been a lack of cure and, therefore, the emotional pain of knowing the inevitable outcome is greater than the burden of not knowing [59]. Parental decisions to initiate genetic testing in asymptomatic minors deny them their ability to weigh these pros and cons and take away their right to decline testing.

Parental Opinions

Balancing the perceived risks of predictive genetic testing in minors with the desires of parents to do what they believe is in the best interest of their child and their family can be difficult, especially when parents are the ones affected. Several studies have investigated parental opinions regarding predictive genetic testing for various conditions. Familial adenomatous polyposis (FAP) is a hereditary cancer syndrome characterized by hundreds of colon polyps and a very high risk for colon cancer if left untreated. Parents of children at risk of inheriting FAP have cited seeking out increased surveillance measures and prophylactic options as reasons for supporting genetic testing in children [60]. Screening recommendations for FAP include initiating annual colonoscopies beginning at age ten, since the average age of onset of colon polyps is around 16 years [61]. Therefore, a second commonly cited reason for genetic testing is to prevent unnecessary screening in children who test negative. Other reasons parents have cited for genetic testing include reducing anxiety and increasing knowledge [59] [60] [62].

In contrast to FAP, parents of children at risk of developing hereditary breast and ovarian cancer generally support postponing genetic testing until adulthood. Hereditary breast and ovarian cancer is characterized by up to an 87% lifetime risk of breast cancer and up to a 44% risk of ovarian cancer [63]. Screening is usually recommended beginning at age 25 or at 5 to 10 years earlier than the youngest age of diagnosis in the family. A study of *BRCA* mutation carriers by Bradbury et al. [64] found that 55% were completely opposed to genetic testing in minors with the most commonly cited reasons being that there is no medical indication for testing (46%), that it would cause fear and anxiety (46%), and that minors are not mature enough for the information (46%). Twenty-four percent indicated that genetic testing should only be considered in minors under specific circumstances with the most common situations being that the child is exceptionally mature (39%) and there is a potential medical risk that

could be mitigated by knowing the result of the genetic test (33%). The overall consensus among parents who are *BRCA1/2*-mutation carriers is that due to the later age of onset for HBOC, genetic testing in most circumstances should be deferred until adulthood when children are mature enough to make their own decisions.

Borry et al. [65] reviewed 14 sets of guidelines from 24 professional organizations about carrier testing (i.e. testing for information on reproductive risk rather than personal medical risk) in minors and found that the majority of guidelines endorsed not performing carrier testing in children but rather deferring testing until a time when children can give adequate informed consent. Although many guidelines established a critical difference between childhood and adolescence in regard to the ability to provide adequate informed consent, few established an exact age at which a child should make their own decisions about testing and stated that it depended on the maturity of the child. However, many guidelines and authors have pointed out that carrier status can have an effect on future offspring and therefore consider reproductive age, as opposed to legal adulthood, as an appropriate age for young persons to give informed consent regarding carrier testing.

With regard to hemophilia A and B, which are X-linked conditions, parents may be more inclined to favor genetic testing at a younger age with one study reporting a majority (84%) of parents wanting their daughters to be tested before age 14 [66]. In this study, the primary reason parents who supported genetic testing at a younger age gave was to enable their daughters to prepare for their own future children. Given the *de novo* rate of hemophilia, many mothers are not aware they are carriers until they have a son who is diagnosed with hemophilia. It is important to note, however, that girls who are carriers of X-linked conditions can exhibit some symptoms due to skewed X-inactivation. Therefore, genetic testing for minors at risk of being a carrier for hemophilia is not always presymptomatic. This is similar to patients with MEN1 who may not show any medically harmful symptoms of disease until they are older than

18 years, but it is not uncommon for patients to begin to show signs such as PHPT at an earlier age.

To our knowledge, no studies have investigated parental preferences regarding MEN1 genetic testing in minors. Two studies examining the quality of life for patients with MEN1 highlighted the challenges of the condition including physical and psychological pain, guilt and an overall pessimistic outlook [67] [68]. However, it has also been reported that patients with MEN1 develop adequate coping mechanisms and tend to adjust well to their situation. Currently, decisions about MEN1 genetic testing in minors is based on individual physician's discretion. Assessing the opinions of patients with MEN1 will provide important insight from those who have first-hand experience of the condition.

The aim of this study is to evaluate attitudes about MEN1 genetic testing for healthy minors among adults with an MEN1 diagnosis and/or their partners. We hypothesize that affected participants will be more likely to favor genetic testing in minors than their partners or spouses and that those with a younger age of diagnosis will be more likely to favor genetic testing in minors than patients with an older age of diagnosis. Findings from this study may help physicians and genetic counselors to better counsel their patients about an appropriate age for testing.

Materials and methods

This cross-sectional study was designed to evaluate attitudes towards predictive *MEN1* genetic testing in healthy minors among individuals at risk of having a child with MEN1. This study was approved by the MD Anderson Cancer Center's (MDACC) Institutional Review Board (2006-0783) and the Committee for the Protection of the Human Subjects at the University of Texas Health Science Center (HSC-MS-11-0433).

Study Population

Study participants were recruited from two sources. One hundred nine eligible patients with MEN1 were identified from a database maintained by the Department of Surgical Endocrinology at MDACC. Eligible patients were able to read and write in English, were age 18 years or older, and had an identified mutation in the *MEN1* gene. Additionally, MEN1 patients were asked to invite their spouses or long-term partners to participate in the study. Eligible spouses and long-term partners also were above the age of 18 and were able read or write in English.

Participants also were recruited from an online advertisement through the online Association for Multiple Endocrine Neoplasia Disorders (A.M.E.N.D.) support group. These participants were directed to an online version of the questionnaire. Eligibility was confirmed through a series of screening questions prior to beginning the questionnaire. Persons with an *MEN1* genetic mutation and their spouses or partners were invited to participate. Individuals who stated they did not have a confirmed *MEN1* mutation were excluded from the study.

Data Collection

Eligible patients from the MDACC database received a study packet by mail. Each packet contained a cover letter (Appendix A), a questionnaire for the affected participant printed on white paper (Appendix B), a questionnaire for the affected participant's spouse or long-term partner printed on yellow paper (Appendix C), and two postage-paid business reply envelopes. The cover letter included a description of the study, a link to the online version of the questionnaire, and directions for both the MEN1-affected participant and partner to complete and return the questionnaire. Packets were mailed only to affected individuals, who were given the option of distributing it to the partner or co-parent they felt most appropriate to complete the questionnaire. Each questionnaire was de-identified, but was coded with an identification number for tracking purposes and to match questionnaires from affected participants with their spouse/partner. MDACC patients who completed the online version of the questionnaire were asked to provide their tracking number. Both the online questionnaire and the paper questionnaire contained the standard questionnaire consent paragraph approved by the MDACC IRB.

Study packets were mailed in mid-December, 2011. A second packet with a reminder letter (Appendix D), two business reply envelopes, and a second copy of each questionnaire was mailed to participants six weeks after the initial mailing. In addition, an advertisement containing a link to an online version of the questionnaire was posted on the A.M.E.N.D. website under its research section in mid-December, 2011. Data collection was completed on February 23, 2012.

The online version of the questionnaire was developed using SurveyMonkey®, a confidential, online survey-making tool. Those who completed the online questionnaire were

required to provide informed consent and confirm eligibility through a series of preliminary questions. Once eligibility was confirmed, participants were directed to the online questionnaire, which was identical to the paper version.

Measures

The study questionnaire was comprised of six sections, which included several validated measures as well as tools adapted from previous studies. The six sections included 1) demographic characteristics of the MEN1-affected participant or partner and the MEN1-related medical history (MEN1 patients only); 2) demographic and MEN1-related medical history of the participant's children; 3) knowledge of MEN1-associated risks and inheritance; 4) the Impact of Event Scale to assess distress response related to an MEN1 diagnosis; 5) the Pediatric Testing Attitudes Scale (P-TAS) to measure attitudes towards predictive testing in minors; 6) a decisional balance measure weighing the pros and cons of genetic testing in minors. The questionnaire also included an open-ended, free hand response question asking participants to identify their perceived ideal age for genetic testing and reasons for selecting the age.

Demographic information

For each participant, we assessed age, gender, country of residence, marital status, highest level of education completed, occupational status, and household income. Partners were asked to identify their relationship to the affected individual and any at-risk children. Affected participants self-reported the type of tumor with which they had been diagnosed (parathyroid, pituitary or pancreatic/stomach/intestinal) and at what age. They were also asked if any tumor had metastasized and what age they were when they were first diagnosed with MEN1.

Family History Information

All participants were asked to identify the number of people in their family that were affected with MEN1, how many people in their family had died from complications related to MEN1, how many people in their family had been diagnosed with an MEN1-related tumor before age 18, and their perceived severity of MEN1 in the family. Perceived severity was measured on a Likert scale ranging from 1 (not at all) to 5 (greatly).

Demographic and medical history also was collected for at-risk children. For participants recruited from MDACC, only affected participants were asked to complete the section about their children and their responses were linked to their corresponding partner's ID number. Data collected included age, gender, diagnosis of a MEN1-related tumor and at what age, age and results of child's genetic testing, and communication of the family's MEN1 status with the child. Participants were asked to complete these questions for each of their children.

Knowledge

To assess the participants' understanding of the natural history and inheritance of MEN1, participants were asked to answer true, false or unsure to eight statements about MEN1. Scores were summarized as the number correct out of the total. After data collection was completed, it was determined that the following item was ambiguous, and therefore was not included in the data analysis: "A person who carries an altered MEN1 susceptibility gene will definitely develop features of MEN1 in his or her lifetime."

Impact of Event Scale

The Impact of Event Scale was designed by Horowitz, et al. [69] as a measure of distress responses anchored to a specific event. This scale includes 15 items that assess both

avoidance and intrusion responses to a specific event. Intrusion was characterized by the presence of unintentional thoughts, dreams, and images, as well as waves of emotion. Avoidance includes denial of the impact of an event, feelings of numbness, and behavioral inhibition. It has been commonly used to assess levels of post-traumatic stress in various groups of patients. The Impact of Event scale was used in this study based on clinical observations of high levels of anxiety in patients with MEN1 and studies that have found patients with MEN1 to have an overall pessimistic outlook [67] [68]. Participants in this study were asked to think about their experience with MEN1 in the family and indicate how often each item had happened to them in the past seven days. Responses were measured on a 4-point scale ranging from not at all to often. Higher scores indicated higher levels of distress related to an MEN1 diagnosis.

Decisional Balance

The decisional balance scale is a component of the transtheoretical model (TTM), which is a conceptual framework often used in health promotion and behavioral change studies to assess a participant's willingness to adopt a new health behavior. One component of the TTM is the stage of change construct which identifies a participant's degree, or stage of readiness to adopt a target behavior and generally includes the following: precontemplation, contemplation, preparation, action, maintenance and termination[70] [71]. Decisional balance is a second component of the TTM framework and is aimed at understanding the importance of pros and cons of a given behavioral change to the participant [72]. The decisional balance may vary depending on an individual's stage of readiness to change: at contemplation, the pros of undertaking a specific behavior change may be weighed equally with the cons of doing so; whereas, in

later stages, when a participant is more likely to change their behavior, the pros are more likely to outweigh the cons [73].

The decisional balance measure used in this study included items describing pros and cons that addressed considerations related to genetic testing in healthy minors and was adapted from measures used in previous studies about genetic testing [74] [75]. Fourteen items were included (seven perceived pros and seven perceived cons). Participants were asked to rate the level of importance for each factor on a 5-point Likert scale (1=not important, 5=very important) when considering having their child tested for MEN1. Higher scores on the decisional balance suggest that the pros outweigh the cons in decision making, whereas lower scores indicate a stronger view of the negative consequences of genetic testing.

Pediatric Testing Attitudes Scale (P-TAS)

The Pediatric Testing Attitudes Scale (P-TAS) was used to measure participants' attitudes about predictive MEN1 testing in minors. The scale was originally created by Peshkin et al. [76] to measure parents' opinions about genetic testing in minors for hereditary breast and ovarian cancer (*BRCA1/2*). For our purposes, the questions were adapted to apply to MEN1. The P-TAS scale is an 11-item measure that comprises two factors: Attitudes and Beliefs (odd numbered items) and Decision Making and Communication (even numbered items). Items measuring attitudes and beliefs are intended to capture parents' theoretical opinions about genetic testing while the decision making and communication items describe the importance of involving the child and others in the decision to have genetic testing and disclosure of the results. Participants were asked to rate their responses from 1 to 5 (1 = strongly disagree and 5 = strongly agree) for each item. Higher scores on the P-TAS measure indicated stronger preferences towards predictive testing in minors.

Ideal Age for Testing

A single item, open-ended question asked respondents what their opinion regarding the ideal age for predictive MEN1 genetic testing was and why they chose this age (Appendix E). This item was also used to capture any additional comments about an appropriate age for genetic testing.

Data Analysis

Summary statistics (i.e. mean, percent, range, SD) were computed for all demographic, medical, and family history variables. Knowledge scores were calculated as the percent correctly answered. Each response from the IES scale was summarized with point values 0, 1, 3, and 5 and scores were calculated separately for the Intrusion and Avoidance subscales and for the overall measure. Possible scores could range from 0 to 35 for the Intrusion subscale, from 0 to 40 for the Avoidance subscale, and 0 to 75 for overall IES score. The decisional balance measure in this study was adapted from a previously developed measure [75]. The decisional balance score was first calculated by subtracting the sum of cons items from the sum of pros items. Raw scores were converted into T scores with a mean of 50 and a standard deviation of 10 for further analysis. Overall decisional balance scores were calculated by subtracting T scores of the cons from T scores of the pros. Participants were given the option of skipping questions they were uncomfortable with and so response rates varied by question. Missing data in the knowledge section was coded as false. Missing questions in the IES, Decisional Balance and P-TAS were replaced with the average score from the other questions answered in the same subscale.

Scores for each factor of the P-TAS measure were calculated independently and jointly as a total P-TAS score. For Factor 1 (Attitudes and Beliefs) and Factor 2 (Decision Making

and Communication), the possible range of scores was 6 to 30 and 5 to 25, respectively. The possible range for total PTAS score was 11 to 55.

For the ideal age, because many participants gave a range of ages (i.e. 8-10) or vague description (i.e. before puberty, when the child is old enough to understand, at a young age, etc.) this item could not be analyzed as a continuous variable. For purposes of analysis, ideal age was coded as either childhood (≤14 years), high school and above (>14 years), or indeterminate by two independent reviewers. Responses such as "as soon as possible" and "before puberty" were included in the ≤14 category. Age 14 was chosen as the cutoff given that this is the age when most children have already started undergoing puberty, are entering high school and have entered the transition period between childhood and adulthood, and are taking on additional adult roles and decision making.

The main outcomes of interest included 1) overall attitude toward MEN1 genetic testing (P-TAS score) and 2) ideal age to perform genetic testing. Predictor variables included spouse vs. affected patient, demographics, medical history (affected participants only), family history characteristics, knowledge of MEN1 genetics, and IES and decisional balance scores. Most demographic data were dichotomized into categorical variables (i.e. residence in the United States vs. other, college graduate and above vs. other, income ≤$75,000 vs. >$75,000, etc). Age, knowledge, IES scores and decisional balance were analyzed as continuous variables. Age was also examined as a dichotomous variable (age younger than 50 years vs. older than 50 years). All analyses were performed using Statistical Analysis System (SAS) software (version 9.2; SAS Institute Inc, Cary, NC). Pearson's correlation coefficients were calculated to compare responses from affected participants to those of spouses. Data analysis was performed separately for affected participants and partners, as well as for both combined. For ease of data presentation, we report the results from the combined analysis and comment where there were

differences when the data was analyzed separately. For the combined data set, the effect of the predictive variables on the two outcomes of interest was examined using generalized linear mixed model analyses in order to account for non-independence between patient and spouse. When patients and spouses were analyzed separately, a general linear model was used to analyze the relationship between predictor variables and P-TAS scores. A general logistic regression analysis was used to evaluate the relationship between the predictor variables and ideal testing age. P-values less than or equal to 0.05 were considered significant. A multivariate model with backward elimination technique using GLIMMIX in SAS was used to obtain adjusted odds ratios for ideal testing age and adjusted beta coefficients for overall P-TAS scores. Variables that were associated with Ideal Age and P-TAS scores in the univariate analysis ($p \leq 0.25$) were used as covariates in the multivariate analysis. Characteristics of the children were not used in the multivariate analysis due to significant multicollinearity with other predictive variables. Multivariate regression models were used to analyze outcomes in parents and spouses separately.

Additionally, the free response for ideal age were independently coded by two reviewers with training in genetic counseling and analyzed to identify common reasons in favor or against MEN1 genetic testing in healthy minors. In many cases, participants had responses that could be assigned to more than one category.

Results

Of the 109 study questionnaires mailed, 10 questionnaires were returned due to inaccurate addresses leaving a denominator of 99 affected participants. It is unclear how many people viewed the online advertisement. A total of 80 participants completed this questionnaire through the two recruitment strategies; forty-nine (31 affected participants and 18 partners) from MDACC and thirty-one (27 affected participants and 4 partners) from the online advertisement. Fifty-eight respondents (73%) had a known mutation in the *MEN1* gene whereas 22 respondents were partners or co-parents of someone with an *MEN1* genetic mutation. Among the spouses or partners, one (5%) stated they were previously married to someone with an *MEN1* genetic mutation and one (5%) had either step-children or adopted children at risk of developing MEN1. All other partners were either currently married to someone with MEN1 or had biological children at risk of developing MEN1.

Demographics

The demographic characteristics of the study population are summarized in Table 1. The average age of all respondents was 47.11 years (SD=14.13) with a range of 19 to 76 years. The majority of respondents were female (60%) and married (77%). Fifty-seven percent had an education level of college degree or greater with 16% achieving an upper level degree. Almost half of participants (49%) were employed full time and 44% had a combined annual salary greater than $75,000. Patients recruited online were from several countries around the world. Although all patients recruited from the MDACC database were from the United States, A.M.E.N.D is an international support group based out of the United Kingdom and had members from many countries. Fifty-five (69%) participants were from the United States and 18 (23%) were from the United Kingdom. Two (3%) respondents were from Canada and there

was one (1%) participant from each of the following countries: Germany, Israel, Netherlands, New Zealand.

Table 1. Participants Demographic Characteristics

Demographics					
	n	**%**			
Affected Participants	58	73%			
Spouses/Partners	22	28%			
Age: Mean (range)	47.11 (19-76)				
Gender	**n**	**%**	**Highest Level of education***	**n**	**%**
Males	32	40%	Some High School	4	5%
Females	48	60%	High School Graduate	5	6%
Residence*			Some College	25	32%
USA	55	70%	College Graduate	25	32%
Other	24	30%	Associate's Degree	7	9%
Marital Status*			Upper Level Degree	13	16%
Single	10	13%	**Occupation***		
Married	61	77%	Employed (Full Time)	39	49%
Separated	2	3%	Employed (Part Time)	8	10%
Divorced	6	8%	Unemployed (Not seeking)	4	5%
Income**			Unemployed (Seeking a job)	1	1%
<$25,000	12	16%	Homemaker	11	14%
$25,000-$50,000	8	11%	Student	4	5%
$50,000-$75,000	18	25%	Retired	12	15%
>$75,000	35	48%			
*** 1 respondent did not answer this question**					
**** 7 respondents did not answer this question**					

Medical History of Participants with MEN1

The self-reported medical history of the affected participants is summarized in Table 2. Only one participant reported no history of an MEN1-related tumor. Most (77%) had more than one affected gland. The average age of diagnosis for each tumor, as well as age of MEN1 diagnosis, was in the late 20s-30s. The minority (14%) was diagnosed with MEN1 before age 18 years.

Table 2. Medical History Characteristics for Participants Affected with MEN1 (n = 58)

Tumor Site	**N**	**%**	**Avg. age, years (Range)**
Parathyroid	52	90%	32.39 (11-66)
Pituitary	22	38%	29.82 (15-57)
Pancreatic/Gastrointestinal	42	72%	37.00 (10-66)
Metastasized tumor	13	31%	
Number of affected sites			
0	1	2%	
1	12	21%	
2	31	53%	
3	14	24%	
Avg. Age of MEN1 Diagnosis (range)			33.66 (10-71)
Diagnosed <18 years	11	14%	

Family History

The MEN1 family history data reported by affected participants and spouses are summarized in Table 3. Most people reported having at least one affected relative (90%) and over half (55%) had a relative who had passed away from MEN1-related causes. Roughly a quarter (24%) indicated they had a relative who was diagnosed with MEN1 before the age of 18 years. Most (79%) reported that MEN1 had greatly or somewhat greatly affected their family's health and well-being.

Table 3. Participants' Family History of MEN1*

	n	%		n	%
Number of Affected Relatives			**Experienced an MEN1-related Death in a Family Member**	44	55%
None	8	10%	Avg. Age of family member's death (range)	51.79 (25-80)	
1-2	28	35%			
3-4	25	32%	**Had a Relative with an MEN1 Diagnosis under 18 years**	19	24%
5 or more	18	23%	Avg. age of family member's diagnosis (range)	14.32 (10-17)	
			Closest Degree of Relation		
Perceived Severity of MEN1 on Family's Health and Well-Being			First Degree	9	47%
			Second Degree	1	5%
1	2	3%	Third Degree	2	11%
2	6	8%	Unknown	4	21%
3	16	20%			
4	18	23%	**Have Children**	59	74%
5	38	48%			
***Includes family history reported by spouses and affected participants**					
****1 respondent did not answer this question**					
*****2 respondents did not respond to this question**					

Fifty-nine respondents (74%) had at least one child at risk of inheriting MEN1 and reported a total of 92 children. Characteristics of participants with children are described in Table 4 and characteristics of the children are described in Table 5. Sixty-six percent of the participants who had children had at least one child who had had genetic testing for MEN1, although only 29% had a child affected with MEN1 and only 4 (7%) had a child diagnosed before age 18. The reported children ranged in age from 0-56 (M= 20.57 years; SD=14.82) and only 24% had been diagnosed with MEN1. Of the 66% of the children who had *MEN1* genetic testing, roughly half (52%) were found to be positive. Age at testing was slightly younger than age of diagnosis of an MEN1-related tumor (M=14.82 vs. M=19.89 years). Participants were also asked whether or not their children had been told about the MEN1 diagnosis in the family and 75% responded that they had.

Table 4. Characteristics of Participants with Children*

	n	%
Child <18 years	28	48%
Child Diagnosed with MEN1	17	29%
Child Diagnosed with MEN1 < 18 years	4	7%
Child had genetic testing for MEN1	38	66%
Child had genetic testing for MEN1 <18 years	21	36%
Child had a positive genetic test for MEN1	24	41%
Child told about MEN1 diagnosis <18 years	21	36%

*Table represents participants who had at least one child in each category.

Table 5. Characteristics of 92 Children Reported by Participants Affected with MEN1

Average Age: 20.567 (0-56)		
Gender	**n**	**%**
Male	50	54%
Diagnosis of MEN1-related tumor		
Yes	22	24%
Avg. Age of diagnosis: 19.889 (3-40)		
Genetic Testing for MEN1		
Yes	61	66%
Positive	32	52%
Avg. Age of Testing: 14.820 (0-43)		
Child Told about Family History of MEN1		
Yes	59	75%
Avg. Age of disclosure 17.587 (3-42)		

Knowledge

The mean knowledge score was 82.86% (*SD*=18.38; Table 6). Thirty-three participants (41%) answered all seven questions correctly and 64% scored higher than 75% correct.

The knowledge scale initially was designed to include 8 questions, with one that read, "A person who carries an altered MEN1 susceptibility gene will definitely develop features of MEN1 in his or her lifetime." Only 30% of participants selected true for this item and of those who responded false, several wrote that it was very likely. Due to the ambiguous phrasing of

the question, this item was dropped from the final analysis as it did not accurately assess the participants' understanding of MEN1 inheritance or natural history.

Table 6. Responses to Knowledge Questions

	True		False		Unsure	
	n	%	n	%	n	%
An altered MEN1 susceptibility gene can be inherited from either parent.	69	86%	9	11%	2	3%
If Lisa looks more like her mother than her father, she has probably received more of her genetic information from her mother.	13	16%	57	71%	10	13%
Susan is the first born in her family. Her mother, who has MEN1, was also the first born. Thus, Susan has a higher risk of developing MEN1 than her younger brothers and sisters.	5	6%	66	83%	9	11%
Rick has had genetic testing for an MEN1 gene alteration that was found in his family. His results were negative; therefore, he is not at increased risk to develop features of MEN1.	65	81%	8	10%	7	9%
Kelly has had genetic testing for an MEN1 gene alteration that was found in her family. Her results were negative; therefore, her children are not at risk to inherit MEN1 from her.	54	68%	22	28%	3	4%
John's father has an altered MEN1 gene. The chance that John has inherited this gene alteration is 50% or 1 in 2.	75	95%	0	0%	4	5%
Once a gene alteration has been detected in a person with MEN1, their family members can be tested for the gene alteration to know for certain whether or not they also have MEN1.	78	98%	1	1%	1	1%
Total Score Avg.: 82.86 (SD=18.382, range=28.571 – 100)						

Impact of Event Scale

Respondents' mean scores on the Intrusion subscale was 11.21 (SD=8.84, range 0-35). Mean score on the Avoidance subscale was 10.93 (SD=8.31, range=0-32). The overall mean IES score was 22.14 (SD=15.58) and ranged from 0 to 58 (maximum possible was 75). In 1999, Corneil, et al. [77] categorized IES scores into clinically meaningful ranges of distress. In our study, 22 out of 80 participants fell within the subclinical distress range (scores 0-8), 22 were classified as in the mild range (9-25), 29 were in the moderate range (26-43) and 7 were classified as falling within the severe range (44+). Response rates per question are presented in Table 7. Between affected participants and their partners, Intrusion subscale ($r=0.022$, $p=0.935$) and total IES ($r=0.234$, $p=0.383$) scores were not significantly correlated, but there was a significant positive correlation between these groups for the Avoidance subscale mean scores ($r=0.544$, $p=0.029$).

Table 7. Responses to Impact of Event Scale

	Not at all		Rarely		Sometimes		Often	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
I thought about it when I didn't mean to.	14	18%	15	19%	33	41%	18	23%
I avoided letting myself get upset when I thought about it or was reminded of it.	12	15%	13	17%	35	45%	18	23%
I tried to remove it from my memory.	36	46%	16	20%	18	23%	9	11%
I had trouble falling asleep or staying asleep because of pictures or thoughts about it that came into my mind.	36	45%	23	29%	15	19%	6	8%
I had waves of strong feelings about it.	20	25%	22	28%	27	34%	10	13%
I had dreams about it.	51	64%	21	26%	6	8%	2	3%
I stayed away from reminders of it.	47	59%	22	28%	8	10%	2	3%
I felt as if it hadn't happened to me or it wasn't real.	49	62%	20	25%	8	10%	2	3%
I tried not to talk about it.	44	55%	10	13%	21	26%	5	6%
Pictures about it popped into my mind.	34	43%	16	20%	21	27%	8	10%
Other things kept making me think about it.	30	38%	19	24%	20	25%	11	14%
I was aware that I still had a lot of feelings about it, but I didn't deal with them.	36	45%	19	24%	21	26%	4	5%
I tried not to think about it.	33	42%	13	16%	26	33%	7	9%
Any reminder brought back feelings about it.	31	39%	14	18%	25	31%	10	13%
My feelings about it were kind of numb.	39	49%	13	16%	21	27%	6	8%
Avg. Total IES: 22.14 (SD=15.58, range=0-58)								
Avg. Intrusion score: 11.21 (SD=8.84, range=0-35)								
Avg. Avoidance score: 10.93 (SD=8.31, range=0-32)								

Decisional Balance

On the decisional balance measure, the mean pros score was 30.17 (SD=4.80) and that of cons was 17.55 (SD=5.56). The mean difference between pros and cons (decisional balance) was 12.21 (SD=6.67), and did not differ for affected participants and spouses when analyzed separately: (M=12.16, SD=6.77; M=12.34, SD=6.59, respectively). Although two affected participants had a score of 0, no participants had a negative decisional balance score.

Table 8. Responses by Question of Decisional Balance

	Not Important		**Slightly Important**		**Somewhat Important**		**Important**		**Very Important**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
I would be relieved to know my child did not have MEN1	0	0%	3	4%	2	3%	18	23%	55	71%
My own experience with MEN1 makes me more concerned about my child's risk for the disease	2	3%	3	4%	5	6%	23	29%	45	58%
I'm afraid I would get too upset	34	42%	17	22%	15	19%	8	10%	5	6%
I / My child could plan for the future	4	5%	5	6%	6	8%	30	39%	32	42%
I'm afraid my child would get too upset	9	12%	7	9%	30	39%	19	25%	11	14%
I am concerned that having the test might cause problems with my child's insurance	14	18%	4	5%	14	18%	13	16%	31	28%
I am concerned about my family's	37	49%	15	20%	13	17%	7	9%	4	5%

reactions										
I want to learn whether my child is at risk for MEN1	0	0%	5	7%	4	5%	17	22%	50	66%
I am worried about how it would affect my relationship with my child	35	47%	14	19%	12	16%	7	9%	6	8%
I'm not sure if the genetic test is accurate	32	45%	7	9%	12	17%	11	15%	9	%
Something could be done to improve my child's health	0	0%	2	3%	5	7%	17	23%	51	68%
I have a responsibility to let my child know if he/she has MEN1	2	3%	6	8%	7	9%	19	26%	40	54%
I just want to know	7	9%	6	8%	14	18%	12	16%	37	49%
The cost of genetic testing is too expensive for my family to afford	33	45%	7	9%	16	22%	8	11%	10	14%
Avg. Sum of Pros: 30.17 (SD=4.80, range=15-35)										
Avg. Sum of Cons: 17.95 (SD=5.56, range=7-34)										
Avg. Decisional Balance: 12.21 (SD=6.67, range=0-28)										

Pediatric Testing Attitudes Scale (P-TAS) and Correlates

The mean score for Factor 1 (Attitudes and Beliefs) on the P-TAS was 25.4 out of a maximum of 30 (range 7.2-30; SD= 4.97). The mean score for Factor 2 (Decision Making and Communication) was 19.0 out of a maximum of 25 (range 11-25; SD= 3.09) The mean total P-TAS score was 44.40 out of a maximum of 55 (range 19.2-55; SD=7.22). Responses between affected participants and partners were not correlated (Factor1: r=0.35, p=.20; Factor 2: r=0.25, p=.362; Total: r=0.33, p=.225).

Table 9. Responses to P-TAS questionnaire

	Strongly Disagree		**Disagree**		**Neither Agree nor Disagree**		**Agree**		**Strongly Agree**	
	n	**%**	**n**	**%**	**N**	**%**	**N**	**%**	**n**	**%**
Children under age 18 should be given the opportunity to be genetically tested for the MEN1gene alteration	2	3%	2	3%	6	8%	28	35%	41	52%
Parents should decide if their children are allowed to have an MEN1 genetic test or not, even if a doctor disagrees	3	4%	6	8%	11	14%	27	35%	30	39%
Even though some of the conditions associated with MEN1 may not affect people until they reach adulthood, children should still be offered MEN1 genetic testing	2	3%	1	1%	4	5%	30	38%	42	53%
Children should be involved in making the decision about whether or not they have MEN1 genetic testing	4	5%	10	13%	16	20%	32	41%	16	21%
I am in favor of MEN1	2	3%	2	3%	8	10%	26	33%	40	51%

genetic testing for children										
If children are tested and they turn out to carry an MEN1 gene alteration (that is, they test positive), they should be told about their test result immediately	4	5%	23	29%	17	22%	21	27%	14	18%
Even if there is no known prevention for the conditions associated with MEN1, children should be offered MEN1 genetic testing	1	1%	3	4%	7	9%	29	37%	39	49%
If children are tested and they turn out to carry a MEN1 gene alteration (that is, they test positive), then this information should be shared with the child's pediatrician	0	0%	2	3%	8	10%	32	41%	37	46%
I want my child to have genetic testing for MEN1 before age 18	1	1%	2	3%	20	27%	18	24%	33	45%
If children are tested and they turn out not to carry an MEN1 gene alteration (that is, they test negative), they should be told about their test result immediately	2	3%	10	13%	13	16%	26	33%	28	35%
The benefits of children participating in MEN1 genetic testing outweigh the risks	1	1%	4	5%	15	19%	19	25%	38	49%
Total Summed Avg.: 44.40 (SD=7.22, range=19.2-55)										
Attitudes and Beliefs: 25.43 (SD=4.97, range=7.2-30)										
Decision Making and Communication: 18.97 (SD=3.09, range= 11-25)										

Results from the univariate generalized linear mixed model regression analysis of the association between independent variables and subscale and overall P-TAS scores are summarized in Table 10. Younger current age predicted higher P-TAS scores ($\beta = -0.147$, $p = 0.03$) and appeared to be primarily driven by the respondents' Factor 1 scores, rather than Factor 2 scores. Knowledge scores were positively associated with P-TAS scores, ($\beta = 1.789$. $p=0.012$), although this association did not reach levels of statistical significance for spouses alone ($p=0.228$). For family history, P-TAS scores were higher among participants who had more than two relatives affected with MEN1 ($\beta = 3.444$, $p=0.050$). However, the number of relatives diagnosed before age 18, the number of relatives who have had an MEN1-related death, the overall perceived disease severity, and characteristics of participants' children were not associated with overall P-TAS scores. Having at least one child who had genetic testing, regardless of the result or age of testing, was associated with higher Factor 2 (Decision-Making and Communication) scores ($\beta = 0.871$, $p = 0.032$).

Decisional balance scores also were positively associated with both P-TAS factor scores, as well as overall P-TAS score ($\beta = 0.36$, $p<0.0001$). There also was a positive association between the mean pros and P-TAS scores for both factors and total P-TAS ($p=<0.0001$) suggesting that scores of the pros are the driving factor in the decisional balance with regard to opinions about genetic testing.

P-TAS scores between affected participants and spouses were not significantly different. Personal medical history was also not associated with higher P-TAS scores, nor was the number of affected sites. Age of diagnosis trended towards a negative association with Factor 1 scores ($p=0.061$), but was not associated with overall P-TAS scores.

Multivariate analysis for P-TAS scores included the covariates current age, marital status, highest level of education completed, number of affected relatives, and decisional balance (Table 11). This model showed that a positive association between decisional balance and overall P-TAS scores remained statistically significant ($p= 0.0002$) while number of affected relatives was not ($p= 0.07$). Additionally, current age was no longer found to be significant.

Table 10. Generalized Linear Mixed Model for Predictors of P-TAS Scores for All Respondents

	n	Attitudes and Beliefs (Factor 1)		Decision Making and Communication (Factor 2)		Total PTAS	
Demographic and Medical History		**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**
Affected participants	57	0.406 (1.157)	0.731	0.947 (0.731)	0.216	1.444 (1.658)	0.399
Partners	22						
Age		-0.126 (0.039)	**0.006**	-0.019 (0.026)	0.460	-0.147 (0.058)	**0.0248**
Knowledge		1.043 (0.432)	**0.030**	0.741 (0.265)	**0.014**	1.789 (0.619)	**0.012**
Decisional Balance		0.264 (0.036)	**<0.001**	0.091 (0.027)	**0.005**	0.357 (0.055)	**<0.001**
Impact of Event		-0.029 (0.036)	0.432	0.017 (0.023)	0.454	-0.066 (0.093)	0.488
Intrusion		0.014 (0.064)	0.825	0.052 (0.039)	0.208	0.066 (0.093)	0.488
Avoidance		-0.123 (0.064)	0.092	0.002 (0.043)	0.967	-0.121 (0.100)	0.244
Number of affected relatives		2.134 (1.110)	0.075	1.170 (0.700)	0.117	3.444 (1.605)	**0.050**
≤2	35						
>2	48						
Age of Diagnosis*		-0.077 (0.040)	0.061	-0.007 (0.027)	0.798	-0.084 (0.061)	0.175
Children		1.462 (1.306)	0.282	0.309 (0.813)	0.710	1.782 (1.903)	0.365
Yes	59						
No	20						
Child with Genetic Testing		1.555 (1.202)	0.218	2.089 (0.871)	**0.032**	3.567 (1.814)	0.071
Yes	38						
No	20						
Child tested before 18 years		2.888 (1.345)	0.069	-0.297 (1.127)	0.800	2.854 (2.219)	0.240
Yes	21						
No	13						

* Calculated for affected participants only using a general linear model.

Table 11. Multivariate Analysis of Predictors for Total P-TAS Scores

	Adjusted-Beta (SE)	p-value
Current Age	-0.076 (0.054)	0.188
Married/Long-term Partner	2.408 (1.707)	0.186
College Graduate or higher	-2.461 (1.375)	0.101
Greater than 2 affected relatives	2.700 (1.344)	0.070
Decisional Balance	0.320 (0.057)	**0.0002**

Ideal Age for Genetic Testing

Overall, 44 participants felt the ideal age for genetic testing for MEN1 should be younger than 14 years and 18 participants felt the ideal age for testing was older than 14 years. Eighteen participants did not respond or provided answers that could not be coded as younger than or older than 14 and were not included in the analyses.

Older participants were more likely to favor testing over the age of 14 (p=0.026). When current age was dichotomized between younger than and older than 50 years, the odds of a participant over 50 years favoring genetic testing after age 14 was 5.33 times higher compared to those under the age of 50 (p=0.025).

Participants who had a lower mean decisional balance score were more likely to support testing at ages older than 14 (p=0.0267). Similar responses were seen in partners alone (p=0.039) and responses for affected participants followed a similar yet not significant trend (p=0.060). Overall, participants whose mean pros scores were lower were more likely to select an age greater than 14 for genetic testing (p=0.027).

Among affected participants only, those with higher mean knowledge scores favored genetic testing before age 14 compared with patients with lower mean knowledge scores (p=0.034). A similar positive trend was also found for the combined dataset (p=0.0523)

The majority of affected participants (73%) favored genetic testing in children under the age of 14 years. Similarly, 65% of partners favored genetic testing before age 14 years. However, no statistically significant difference was noted between affected participants and partners with regard to their preference in age for predictive genetic testing. Demographic characteristics including gender, country of residence, marital status, education, employment and income also were not associated with preferred age of testing, nor were personal medical history, including number of affected glands or age of diagnosis, and family history characteristics.

In a multivariate analysis, none of the covariates including current age, highest level of education completed, knowledge, intrusion scores and decisional balance were associated with preferred age for testing, possibly due to the limited sample size. In a separate multivariate logistic regression model including affected participants only, adjusted OR suggest that having an education level of college graduate or higher and being employed were associated with favoring genetic testing after age 14 ($p=0.043$ and $p=0.048$ respectively), whereas higher knowledge scores were associated with favoring genetic testing in children younger than 14 years ($p=0.008$).

Children's wellbeing, genetic testing, and knowledge of MEN1 in the family also were analyzed as predictor variables for respondents with children. None of these predictors reached levels of statistical significance. However, the variable most closely approaching levels of statistical significance was whether or not a child had been diagnosed with MEN1, regardless of age ($p=0.061$). Respondents who do not have a child diagnosed with MEN1 were more in favor of testing children before age 14 years. When affected participants were analyzed separately, they were 6.25 times more likely to support genetic testing in children over the age of 14 if they had a child that was diagnosed with MEN1 ($p=0.034$).

Table 12. Generalized Linear Mixed Model for Continuous Predictors of Ideal Age for All Participants

Demographics and Medical History	% Ideal Age ≤14 years	% Ideal Age >14 years	OR (95% CI)	p-value
Affected Participants	33	12	0.647 (0.144-2.901)	0.528
Partners	11	6		
Current Age				
<50 years	31	5	6.484 (1.338-31.429)	**0.025**
≥50 years	11	6		
Child Diagnosed with MEN1			5.956 (0.900-39.422)	0.061
Yes	6	8		
No	27	6		

Table 13. Generalized Linear Mixed Model for Dichotomous Predictors of Ideal Age for All Participants

Demographic and Medical History	OR (95% CI)	P
Age	1.070 (1.010-1.133)	**0.026**
Knowledge	0.572 (0.325-1.007)	0.053
Decisional Balance	0.572 (0.854-0.988)	**0.027**
Sum of Pros	0.0899 (0.821-0.985)	**0.027**
Sum of Cons	1.028 (0.955-1.108)	0.415
Impact of Event	0.977 (0.930-1.027)	0.322
Intrusion	0.925 (0.841-1.017)	0.097
Avoidance	1.003 (0.915-1.100)	0.936
Age of Diagnosis*	1.037 (0.992-1.083)	0.109

* Calculated for affected participants only using logistic regression analysis.

Table 14. Multivariate analysis for Predictors of Ideal Age (combined data)

	Adjusted OR (95% CI interval)	**P**
Age	1.065 (0.981-1.155)	0.105
College graduate and above	5.441 (0.395-74.88)	0.157
Knowledge	0.534 (0.202-1.412)	0.158
Intrusion	0.906 (0.766-1.073)	0.195
Decisional Balance	0.936 (0.847-1.035)	0.1522

Table 15. Multivariate Analysis for Predictors of Ideal Age (affected participant only)

	Adjusted OR (95% CI interval)	**P**
College graduate and above	15.56 (1.087-222.746)	**0.043**
Employed (full time/part time)	49.974 (1.03->999.99)	**0.048**
Knowledge	0.141 (0.033-0.595)	**0.008**
Age of Diagnosis	1.09 (0.996-1.192)	0.060

Reasons for Testing

Multiple reasons were identified for selecting specific ages and participants frequently gave more than once answer. Nine themes were identified in favor of testing and two were identified against testing. The first theme, "old enough to understand and participate in decision-making," was the most common response (41%) and included answers such as "Old enough to understand the ramifications/consequences," and "Would want the ability to make an informed decision and to be able to manage the consequences mentally and physically." The

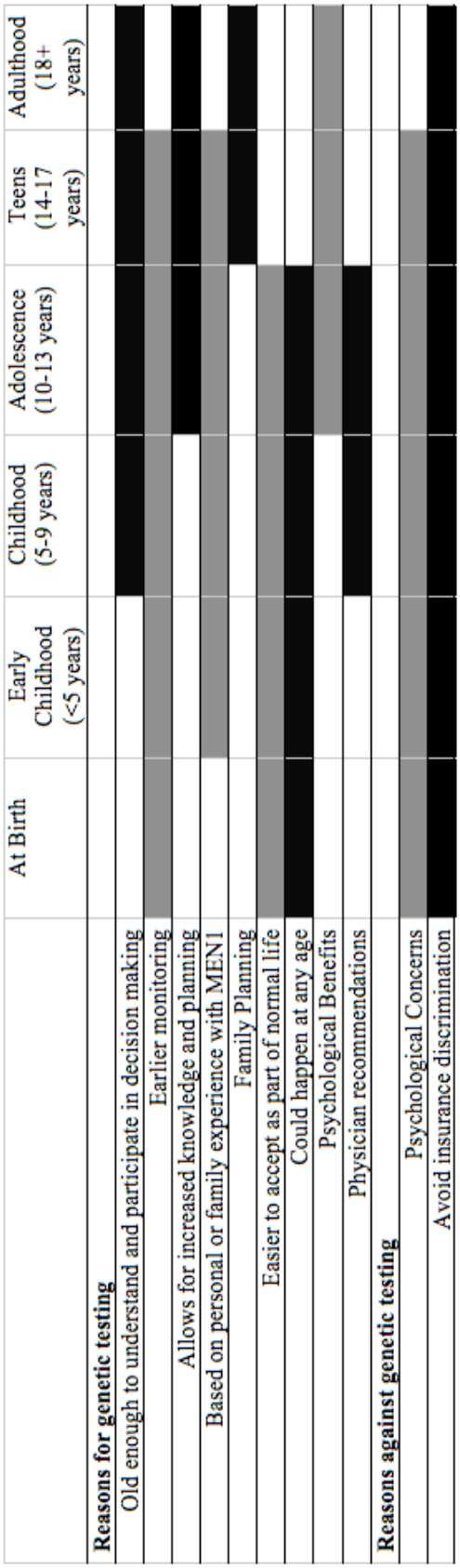
second most common theme was to allow for earlier monitoring of symptoms and tumor markers (14%) and for increased knowledge and planning (14%), including educating local physicians and planning for an appropriate time for treatment. The theme "personal and family experience" (11%) included respondents who selected an age based on when signs of MEN1 first began in their family. Several respondents (6%) who selected a younger age for testing did so to allow the child to accept the diagnosis as part of their normal life, while another 6% who selected older ages acknowledged the benefits of family planning with a diagnosis. Five percent felt genetic testing should be done early because symptoms have been reported in very young children. Three percent of respondents identified psychological benefits from predictive testing, such as reassurance from a negative test result. Only two respondents (3%) stated they selected an ideal age based on local physician recommendations. Several participants identified negative outcomes of genetic testing as reasons for delaying or never having genetic testing. These included psychological concerns at a young age when there is little or no risk (6%) and fears about insurance discrimination (5%). Although all of these reasons were selected by multiple participants, they were often identified at different times in a child's life. Figure 1 shows the distribution of reasons for and against genetic testing at various points in a child's life.

Table 16. Reasons for and Against Genetic Testing*

Reasons for genetic testing	
Old enough to understand and participate in decision making	41%
Earlier monitoring	14%
Allows for increased knowledge and planning	14%
Based on personal or family experience with MEN1	11%
Family Planning	6%
Easier to accept as part of normal life	6%
Could happen at any age	5%
Psychological Benefits	3%
Local recommendations	3%
Reasons against genetic testing	
Psychological Concerns	6%
Avoid insurance discrimination	5%

*Answers are not mutually exclusive

Figure 1. Distribution of Reasons for and Against Genetic Testing Across Age Groups



Discussion

Most published literature about genetic testing in minors are expert opinions from ethicists and although opinions about predictive genetic have been studied in a few other genetic syndromes [59] [60] [62] [64] [66], no studies have examined this question specifically in MEN1. This study sought to determine the attitudes about predictive *MEN1* genetic testing in those at risk of having a child with MEN1. This study was exploratory in nature and opens up several possibilities for future studies and avenues for genetic counseling.

Overall, participants in this study seem to favor genetic testing in minors. Of those who gave specific ages or age ranges, only seven favored delaying testing until after age 18. The P-TAS is a relatively new scale that was previously validated in a population at high risk for a BRCA mutation [76]. Participants in our study had higher scores for each factor and for total P-TAS scores than participants in this original study. This is most likely attributable to the later age of onset of BRCA-related cancers, which almost never present in minors. The fact that participants have relatively high P-TAS scores demonstrates that both affected participants and their partners have opinions about genetic testing more similar to a young onset condition instead of an adult onset condition.

Respondents' age at the time of study completion was found to be a predictor for attitudes about genetic testing in most of the completed analyses with older participants more likely to favor postponing genetic testing until children are older. Older patients may be more likely to have experienced the effects of MEN1 for longer periods of time either in themselves or in their families. They may also be more aware of the long-term psychological effects that come from aging with MEN1, having been diagnosed and adjusted to the diagnosis themselves. Prior to the availability of *MEN1* genetic testing, diagnoses were made on a clinical basis.

With advances in genetic technology, this younger generation of at risk individuals will be the first to have predictive testing available to them. Therefore, older participants may also be drawing on their own experiences with genetic testing when considering the most appropriate age for predictive testing. It is also likely that younger participants may have benefitted from earlier genetic testing and/or medical surveillance than older participants, and this might be influencing their opinions about the ideal age to have genetic testing.

Reasons given for genetic testing at an older age seemed to be strongly focused on psychological reasons, including the age at which the child can understand and participate, knowledge and planning, and family planning. On the other hand, many participants who favored younger ages for testing, including at birth, early childhood and childhood, found the perceived medical benefits of testing to be the predominant factor in their decision making about the ideal age to test, which is consistent with previous findings in the literature [52] [53] [54] [55]. A second predictor, knowledge of MEN1 genetics, suggests that patients with a better understanding of MEN1 favor genetic testing in minors. This may also suggest that patients with increased knowledge scores may be more focused on these medical effects and the opportunity for increased screening over the psychological concerns.

A third predictor for opinions about genetic testing was the number of affected relatives in a family. Participants with two or more affected relatives were also more likely to favor genetic testing in minors. Although this variable fell out of significance during the multivariate analysis, it does point towards a possible trend in family history and suggests that increased exposure throughout a family may be contributing to opinions favoring a younger age for genetic testing. Because no other family history variables were found to be significant predictors, this is an area that may benefit from future research specifically focused on the impact of family history on age of genetic testing.

Finally, decisional balance was consistently found to be a strong predictor of preferences for genetic testing at a younger age. As part of the transtheoretical model, the decisional balances aims to place participants along a spectrum of stage of change related to a health behavior, in this case genetic testing in minors. Participants who perceive the cons as outweighing the pros are less likely to have achieved the action stage of state of change [78]. It would be expected that parents who place a greater emphasis on the positives of genetic testing would be more likely to favor genetic testing in minors and/or pursue genetic testing in their own children, if possible. In fact, participants in this study seemed to have predominantly positive attitudes about genetic testing with a positive association towards testing in minors and ideal age less than 14 years. Additionally, a trend appears to be emerging between participants who have had a child tested for MEN1 and overall P-TAS scores. This might indicate that participants who are in favor of genetic testing in minors are truly having their child tested for MEN1 or encouraging their adult children to do so.

Interestingly, this study also identified several factors that do not predict opinions about genetic testing. Personal medical history does not have a significant impact on opinions about testing. The reported MEN1-specific medical history of this study population is typical of individuals with MEN1 reported in the literature, including tumor prevalence and age of diagnosis [1] [5] [6] [38]. The high penetrance of MEN1-related tumors is also evident given that all but one affected participants reported a history of at least one tumor type. No clear pattern emerged between personal medical factors and attitudes for genetic testing suggesting that opinions vary across patients with MEN1 diagnosed at all ages and with differing degrees of severity.

Additionally, MEN1-related stress (measured with the Impact of Event scale and perceived severity of disease) does not appear to impact opinions about predictive *MEN1*

genetic testing. Although responses appeared to suggest high levels of MEN1-related stress with nearly half of participants scoring in the moderate to severe range for IES and most patients selecting "greatly" for perceived disease severity in the family, neither appeared to predict attitudes about predictive genetic testing in minors. Several studies have examined levels of stress and anxiety and the resulting willingness to seek out medical treatment or genetic testing. Many have shown that patients with high levels of anxiety often seek out frequent medical advice and reassurance [79] [80]. However, other studies have suggested that those at a highest risk or who have already begun to show symptoms are also likely to avoid medical care or postpone presenting to a doctor for fear of the emotional repercussions of a diagnosis or genetic testing [81] [82]. Therefore, it is possible that patients with higher IES scores and perceived severity may act in either way with regards to seeking out genetic testing for themselves or their children.

As an exploratory study, it is particularly interesting to note the reasons that participants provided for selecting specific ideal ages for MEN1 genetic testing. With certain exceptions, psychological effects seem to be a driving factor in choosing later ages for genetic testing, while perceived medical benefits seem to be driving factors at a younger age. A handful of patients selected multiple ages that often varied significantly. For example, one participant selected ages 10-12 based on the medical effect it can have during the teenage years but also selected 25 years and older because of the potential difficulty of obtaining health insurance. These varied responses further emphasize the lack of clear consensus for when testing should be performed and also highlight the idea that patients views may be highly conflicted.

Several of the reasons provided in response to this questionnaire matched opinions and concerns expressed in the literature. The most common reason cited was an age at which children can understand the implications of genetic testing. This is a sentiment that mirrors

opinions in professional statements about genetic testing in minors for conditions of unknown significance, which emphasize the importance of involving the child and family in the decision making process [50] [51]. Several authors who support testing at a young age indicated that it would give the child time to accept the diagnosis and adjust to it being part of their everyday life [54]. This sentiment was echoed by roughly 6% of participants in this study. Other responses pointed out the enormous psychological burden that could be placed on a child if the test was positive, years before they may begin to show symptoms. This concern has also been addressed by authors exploring the potential impacts on children [52] [53] [57]. Thus, this study exemplifies the varying opinions about the psychological impact of genetic testing and adds data to the ongoing debate about the psychological effects of genetic testing in minors.

Only two participants selected local physician recommendations as their reason for the most appropriate age for genetic testing. Of those who selected local recommendations as a reason for genetic testing, one selected age 5 while the other selected age 10. This again underscores the lack of a clear consensus about the appropriate age for testing. However, the low identification with this reason also demonstrates that what guidelines do exist are either not being expressed to patients and their families, or that patients are forming their own opinions based on additional factors and their own experiences with MEN1.

Fear of insurance discrimination was listed as a major reason against genetic testing, however only cited by a minority of participants. Interestingly, many of the participants who cited this reason were from the UK and stated that it wasn't a concern within the UK, but it would be if they lived in a country without universal healthcare. Unlike the US, the UK has a universal health care system funded by the National Health Service (NHS). Health insurance is guaranteed to every citizen to cover medical care from primary physicians as well as specialists. However many citizens also opt to purchase private medical insurance[83]. In

2009, the Genetic Information Non-discrimination Act [84] was enacted in the United States and prohibits health insurance companies and employers from discriminating or denying coverage based on the results of a genetic test. However, this act does not extend to life insurance or long-term disability insurance. The possibility of genetic discrimination is less significant in countries with a universal health care system. Although there is currently no law in the United Kingdom that mirrors GINA, several interest groups have been created to monitor the progression of genetic testing and its impact on health insurance. A set of moratoriums have been put in place that prohibit insurance companies from raising premiums based on genetic test results [83]. Concern about insurance discrimination has frequently been cited by patients as a limitation for genetic testing in general [85] [86] and many participants in this study were likely tested prior to the initiation of any protective laws, particularly in the United States. It is unclear to what extent the study participants knew about anti-genetic discrimination laws. It may be that some individuals would be reassured if they knew about laws such as GINA which could change their opinion about genetic testing. Indeed, several individuals had stated that they were not sure if any anti-discrimination laws had been passed. Alternately, it may be that people are not reassured that GINA will actually help to protect them and their family members. With the implementation of these laws and other protective measures, it will be interesting to monitor the uptake of genetic testing and see if it alters opinions about genetic testing in minors.

Strengths of Study

Very few studies have investigated the psychological state of patients with MEN1. This study is the first of its kind to investigate opinions about predictive genetic testing in minors. Considering the rarity of MEN1, this was a large sample size that included opinions from around the world. This allowed for opinions from various backgrounds and multiple health

care systems. Additionally, a strength of this study is that it looked directly at the opinions of those at risk of having a child with MEN1 and incorporates responses from both affected participants and co-parents.

Another strength of this study is that most measures used are validated survey tools. The Impact of Event scale is a frequently used measure for post-traumatic stress disorder and the decisional balance has been used to measure stage of change. The Pediatric Testing Attitudes Scale is a relatively new measure that is expected to be used more often in future studies about genetic testing in minors. The use of validated study measures in this study strengthens confidence in the results.

Limitations and Future Studies

The major limitation of this study is that it was a self-administered questionnaire. As such, all medical and family data were self-reported and could not be verified, and the accuracy of the diagnosis of MEN1 could not be assessed in participants recruited from the Internet. However, in reviewing the reported medical histories, all participants were typical of MEN1 patients reported in the literature. Additionally, participants were given the option to skip any questions with which they were uncomfortable, resulting in missing data. Our study was administered to any patient with a positive genetic test result and their spouses or long-term partners. This sample included both patients with and without children. Therefore, some patients were asked to imagine how they would feel about their hypothetical children, which can be difficult for some patients to consider.

Although our sample size was large for the condition, it was still a small sample size from a statistical perspective. Clear trends were evident in the data analysis; but future studies may be able to elucidate further patterns related to a participant's opinions about predictive

genetic testing. Because patients and spouses may have some correlation, a generalized linear mixed model was used for data analysis. However, it is reasonable to assume that spouses may have an influence on each other's opinions that could not be captured in the data analysis.

As understanding of MEN1 and cancer genetics continues to grow and screening technologies improve, it will be important to continually reconsider the most appropriate age for *MEN1* genetic testing. Currently, data into the psychological impact of MEN1 is lacking and further studies may help to elucidate the most important issues for patients living with MEN1. Further studies investigating the opinions of health care professionals and how they counsel families about predictive genetic testing may help to improve guidelines for the most appropriate age for genetic testing. Studies about patients who have had predictive genetic testing themselves may also shed more light on the long-term psychosocial effects, as this will likely be the first generation to have access to predictive genetic testing.

Conclusions and Implications

Our initial hypotheses were that there would be a significant difference between affected participants and spouses and that age of diagnosis would have an impact on the preferred age of predictive testing. While we did not find either of these to be true, we did find several interesting trends. The most significant predictors of favoring genetic testing in minors are younger current age, increased knowledge, two or more affected relatives, and a positive decisional balance. Overall, it was clear that most patients and their spouses felt that MEN1 should be addressed earlier than adult-onset conditions and rather as a syndrome with unknown medical significance at a younger age. Specific considerations for testing in younger children focused primarily on the perceived medical benefits, whereas participants who selected older ages in minors were focused primarily on the psychosocial impacts of genetic testing. These

findings will have several implications for genetic counseling for families at risk of having a child with MEN1. Although this study was not able to elucidate a single age at which genetic testing would be most appropriate, the results of this study may help patients consider multiple viewpoints which may help them determine which factors are most important to them and their families. When discussing genetic testing with patients, it may also be worthwhile to discuss reasons other families have expressed for pursuing genetic testing in children. Among the various responses given, many participants expressed that it was an individual decision for each child and parent involved. Therefore, in selecting the most appropriate age for their child to be tested, parents will likely have the clearest ideas about when their child will be able to understand and deal with the results of a positive genetic test.

APPENDIX A. INVITATION LETTER

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Clinical Cancer Genetics Program
T 713-563-1908 F 713-745-1921
Unit 444
1400 Hermann Pressler Dr
Houston, TX 77030-4008

Date: December 7, 2011

Name:

Address:

Dear Ms./ Mr. <Name>:

We are writing to thank you for your continued participation in our research involving MEN1 and to let you know about a new opportunity. We would like to invite you to take part in a research study entitled *Parental Attitudes of Predictive* MEN1 *Genetic Testing in Minors.* We are interested in learning about your experiences and feelings towards MEN1 genetic testing in healthy children.

We are inviting you to participate because you, your spouse/partner, or a family member was seen for MEN1 at M. D. Anderson Cancer Center. As you know, MEN1 is a rare hereditary condition that increases cancer risk and can be passed on to children. The ideal age for genetic testing in minors who have no symptoms is unclear. We are interested in learning how families with MEN1 feel about having their children genetically tested for MEN1. Participation in this research study is voluntary and involves completing the enclosed survey. The survey should take about 15-20 minutes to complete and there is no cost to participate.

Although your participation in this project may not have direct benefit to you, it will help researchers, doctors and genetic counselors better understand the needs of families with children at risk for MEN1. Some of the questions may be upsetting and you do not have to answer them. If you decide to participate in the study, it is very important that you answer as completely as you can; please feel free to add comments or questions on the survey and we will do our best to respond.

If you would like to participate in this study, please complete the questionnaire that is included in this packet and return it to us in the pre-paid addressed envelope. Patients who have been diagnosed with MEN1, please complete the white survey. Spouses or partners of persons with MEN1 please complete the yellow survey. We are interested in responses from both patients and spouses but responses will still be included even if only one person is available to participate.

If you prefer the online survey, please go to http://www.surveymonkey.com/s/MEN1inminors and follow the instructions. You will need to enter your ID user number, which is <insert ID #>. The online survey has the same questions as the one included in this packet and was created using a professional account on Survey Monkey, which is a confidential survey making tool. Your responses will be strictly confidential and will only be shared with study staff.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Clinical Cancer Genetics Program
T 713-563-1908 F 713-745-1921
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Houston, TX 77030-4008

At the end of the survey, there is a place to write your name and telephone number if you are willing to be contacted with questions about any of your responses. If you have any friends or relatives you think would be interested in participating in the study, a space is available for their contact information so we can send them a copy of this letter as well. Providing contact information is optional, and your name will not be linked with your survey responses, if provided.

Completion of this survey is optional and confidential. Due to the anonymous nature of the study, questionnaires will not be able to be withdrawn once they have been submitted. If you have any questions or would like more information please contact, the Clinical Cancer Genetics Program or your genetic counselor at (713) 745-7391 or e-mail ccg@mdanderson.org.

Thank you very much for considering this invitation to participate in our study.

Sincerely,

Katie Rock, BA
Genetic Counseling Intern

Thereasa Rich, MS, CGC
Genetic Counselor

Elizabeth Grubbs, MD
Assistant Professor

APPENDIX B: AFFECTED PARTICIPANT QUESTIONNARIE

Please fill out this survey if **YOU** have been diagnosed with MEN1 ID#

I have read the description of the study, and I have decided to participate in the research project described here. I understand that I may refuse to answer any (or all) of the questions at this or any time. I understand that my decision about participating in this study or answering questions will not affect the care or services that I receive at M. D. Anderson Cancer Center.

During the course of this study, the research team at The University of Texas M. D. Anderson Cancer Center will be collecting information about me that they may share with health authorities, study monitors who check the accuracy of the information, and individuals who put all the study information together in report form. Information that could identify me personally will not be made public. By answering the questions, I am providing authorization for the research team to use and share my information at any time. If I do not want to authorize the use and disclosure of my information, I may choose not to answer these questions. There is no expiration date for the use of this information as stated in this authorization.

Completion of this survey is optional and confidential. Due to the anonymous nature of the study, questionnaires will not be able to be withdrawn once they have been submitted. If you have any questions or would like more information please contact, the Clinical Cancer Genetics Program or your genetic counselor at 713-745-7391 or e-mail ccg@mdanderson.org. For information on the Notice of Privacy Practices, please call 713-792-2933.

Attitudes Toward MEN1 Genetic Testing in Minors Survey

Instructions: We are interested in learning about your attitudes toward MEN1 genetic testing for healthy children who are under the age of 18. As you may know, the best age for healthy children to undergo MEN1 genetic testing is unknown due to several medical, social, and psychological reasons. We wish to learn about your experience and attitudes toward such testing.

Part 1: The following are questions about YOU.

1. What is your age: _____

2. What is your gender?

   ☐ Male ☐ Female

3. Where do you currently live? State: _____ Country:_____

4. What is your marital status?

   ☐ Single ☐ Married/Long Term Partner ☐ Separated ☐ Divorced ☐ Widowed

5. What is the highest grade or level of schooling you completed?

   ☐ Some high school
   ☐ High school graduate
   ☐ Some college
   ☐ College graduate (4 Year Degree)
   ☐ Associate's degree
   ☐ Upper-level degree

6. What is your current occupational status

☐ Employed (Full Time) ☐ Homemaker
☐ Employed (Part Time) ☐ Student
☐ Unemployed (Not seeking a job) ☐ Retired
☐ Unemployed (Seeking a job)

7. What is your (combined) annual household income?

☐ Less than $25,000 ☐ $50,000 - $75,000
☐ $25,000 - $50,000 ☐ More than $75,000

8. Please check any of the following you've been diagnosed with and write the age you were diagnosed:

☐ Parathyroid gland tumor (hyperparathyroidism); **Age diagnosed**: _____
☐ Pituitary gland tumor (for example, prolactinoma); **Age diagnosed**: ____
☐ Pancreatic/stomach/intestinal tumor (for example, gastrinoma, neuroendocrine tumor); **Age diagnosed: _____**

Has this tumor spread (metastasized)? Yes ☐ No ☐

9. Have you had genetic testing for MEN1?

Yes ☐ No ☐

If yes, was a mutation found (was the test positive)? Yes ☐ No ☐

10. At what age did you first find out you had MEN1 (if you are not sure, just give your best guess)?

_____

11. How many members of your family also have been diagnosed with MEN1?

☐ None
☐ 1-2
☐ 3-4
☐ 5 or more

12. Do you have any relatives who have died from complications of MEN1?

Yes ☐ No ☐

If yes, how old were they when they died? _____

13. How severely do you feel MEN1 has affected your family's health and well-being? (Please circle a number on the scale below).

Not at all		Somewhat		Greatly
1	2	3	4	5

14. Has anyone in your family been diagnosed with an MEN1-related tumor before 18 years of age?

Yes ☐ No ☐ If yes, how old were they? _____

If yes, how are they related to you (for example, sister, cousin, etc.)?

_____

15. Do you have children?

☐ Yes – if yes, please continue to part 2

☐ No – if no, please skip part 2, and continue to part 3

Part 2: Please tell us about each of your children, including your adult children, if applicable
(please only include children who are biologically related to you):

	How old is this child?	Gender	Has this child been diagnosed with any MEN1-related tumors? If yes, how old were they when they were first diagnosed?	Has this child had MEN1 genetic testing? If yes, how old were they when they were tested?	Have you shared your family's diagnosis of MEN1 with this child? If yes, how old were they when you told them?
Child 1		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
Child 2		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
Child 3		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
Child 4		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
Child 5		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
Child 6		Male ☐ Female☐	Yes ☐ No ☐ Age Diagnosed:	Yes ☐ No ☐ Age Tested: Result:	Yes ☐ No ☐ Age Told:
If you have more than 6 children, please use the back of this survey to tell us about them.					

ID#

Part 3: The following questions are intended to find out what people know about cancer and genetic testing so that we can improve our educational efforts. This is not a test. We are simply interested in finding out what the general level of knowledge is regarding these topics. Please indicate whether you think each statement is true or false, or if you don't know.				
16	An altered MEN1 susceptibility gene can be inherited from either parent.	True	False	Unsure
17	If Lisa looks more like her mother than her father, she has probably received more of her genetic information from her mother.	True	False	Unsure
18	A person who carries an altered MEN1 susceptibility gene will definitely develop features of MEN1 in his or her lifetime.	True	False	Unsure
19	Susan is the first born in her family. Her mother, who has MEN1, was also the first born. Thus, Susan has a higher risk of developing MEN1 than her younger brothers and sisters.	True	False	Unsure
20	Rick has had genetic testing for an MEN1 gene alteration that was found in his family. His results were negative; therefore, he is not at increased risk to develop features of MEN1.	True	False	Unsure
21	Kelly has had genetic testing for an MEN1 gene alteration that was found in her family. Her results were negative; therefore, her children are not at risk to inherit MEN1 from her.	True	False	Unsure
22	John's father has an altered MEN1 gene. The chance that John has inherited this gene alteration is 50% or 1 in 2.	True	False	Unsure
23	Once a gene alteration has been detected in a person with MEN1, their family members can be tested for the gene alteration to know for certain whether or not they also have MEN1.	True	False	Unsure

Part 4. Please think about your experience with MEN1 in your family. Please indicate how frequently each comment was true for you <u>during the past seven days.</u>

		Not at all	Rarely	Some times	Often
24	I thought about it when I didn't mean to.	1	2	3	4
25	I avoided letting myself get upset when I thought about it or was reminded of it.	1	2	3	4
26	I tried to remove it from my memory.	1	2	3	4
27	I had trouble falling asleep or staying asleep because of pictures or thoughts about it that came into my mind.	1	2	3	4
28	I had waves of strong feelings about it.	1	2	3	4
29	I had dreams about it.	1	2	3	4
30	I stayed away from reminders of it.	1	2	3	4
31	I felt as if it hadn't happened to me or it wasn't real.	1	2	3	4
32	I tried not to talk about it.	1	2	3	4
33	Pictures about it popped into my mind.	1	2	3	4
34	Other things kept making me think about it.	1	2	3	4
35	I was aware that I still had a lot of feelings about it, but I didn't deal with them.	1	2	3	4
36	I tried not to think about it.	1	2	3	4
37	Any reminder brought back feelings about it.	1	2	3	4
38	My feelings about it were kind of numb.	1	2	3	4

Part 5: The following questions ask about your personal feelings about genetic testing in healthy minors (in other words, individuals with no medical conditions who are younger than age 18). Please indicate your agreement with each of the following statements using the scale below.

		Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
39	Children under age 18 should be given the opportunity to be genetically tested for the MEN1gene alteration	1	2	3	4	5
40	Parents should decide if their children are allowed to have an MEN1 genetic test or not, even if a doctor disagrees	1	2	3	4	5
41	Even though some of the conditions associated with MEN1 may not affect people until they reach adulthood, children should still be offered MEN1 genetic testing	1	2	3	4	5
42	Children should be involved in making the decision about whether or not they have MEN1 genetic testing	1	2	3	4	5
43	I am in favor of MEN1 genetic testing for children	1	2	3	4	5
44	If children are tested and they turn out to carry an MEN1 gene alteration (that is, they test positive), they should be told about their test result immediately	1	2	3	4	5

45	Even if there is no known prevention for the conditions associated with MEN1, children should be offered MEN1 genetic testing	1	2	3	4	5
46	If children are tested and they turn out to carry a MEN1 gene alteration (that is, they test positive), then this information should be shared with the child's pediatrician	1	2	3	4	5
47	I want my child to have genetic testing for MEN1 before age 18	1	2	3	4	5
48	If children are tested and they turn out not to carry an MEN1 gene alteration (that is, they test negative), they should be told about their test result immediately	1	2	3	4	5
49	The benefits of children participating in MEN1 genetic testing outweigh the risks	1	2	3	4	5

Part 6: The following list includes reasons some people give for wanting or not wanting to have their child have genetic testing. Please indicate how important you feel each of the following is in making a decision to have MEN1 genetic testing for your child using the 1-5 point scale.

		Not Important	Slightly Important	Somewhat Important	Important	Very Important
50	I would be relieved to know my child did not have MEN1	1	2	3	4	5
51	My own experience with MEN1 makes me more concerned about my child's risk for the disease	1	2	3	4	5
52	I'm afraid I would get too upset	1	2	3	4	5
53	I / My child could plan for the future	1	2	3	4	5
54	I'm afraid my child would get too upset	1	2	3	4	5
55	I am concerned that having the test might cause problems with my child's insurance	1	2	3	4	5
56	I am concerned about my family's reactions	1	2	3	4	5
57	I want to learn whether my child is at risk for MEN1	1	2	3	4	5
58	I am worried about how it would affect my relationship with my child	1	2	3	4	5
59	I'm not sure if the genetic test is accurate	1	2	3	4	5
60	Something could be done to improve my child's health	1	2	3	4	5
61	I have a responsibility to let my child know if he/she has MEN1	1	2	3	4	5
62	I just want to know	1	2	3	4	5
63	The cost of genetic testing is too expensive for my family to afford	1	2	3	4	5

64. What do you feel is the ideal age for an individual to have MEN1 genetic testing? Why did you choose this age?

Please fill out this survey if **YOU** have been diagnosed with MEN1 ID#

The following questions are optional:

Please indicate if we may contact you by phone with any follow up questions:

Yes No

Name: _____

Phone Number: _____

We would like to include as many people as possible in this survey. Individuals with MEN1 and their spouses/partners are eligible. Please tell us about any friends or relatives who may be interested in participating in our study:

Name: _____

Relationship to you: _____

Email: _____

Phone: _____

Address: _____

_____

_____

Name: _____

Relationship to you: _____

Email: _____

Phone: _____

Address: _____

_____

_____

Thank you very much for completing this questionnaire. The information you have provided has been very helpful and we appreciate your thoughtful answers.

APPENDIX C: SPOUSE/PARTNER QUESTIONNAIRE

Please fill out this survey if you are the **SPOUSE OR PARTNER** of a person with MEN1 ID#

I have read the description of the study, and I have decided to participate in the research project described here. I understand that I may refuse to answer any (or all) of the questions at this or any time. I understand that my decision about participating in this study or answering questions will not affect the care or services that I receive at M. D. Anderson Cancer Center.

During the course of this study, the research team at The University of Texas M. D. Anderson Cancer Center will be collecting information about me that they may share with health authorities, study monitors who check the accuracy of the information, and individuals who put all the study information together in report form. Information that could identify me personally will not be made public. By answering the questions, I am providing authorization for the research team to use and share my information at any time. If I do not want to authorize the use and disclosure of my information, I may choose not to answer these questions. There is no expiration date for the use of this information as stated in this authorization.

Completion of this survey is optional and confidential. Due to the anonymous nature of the study, questionnaires will not be able to be withdrawn once they have been submitted. If you have any questions or would like more information please contact, the Clinical Cancer Genetics Program or your genetic counselor at 713-745-7391 or e-mail ccg@mdanderson.org. For information on the Notice of Privacy Practices, please call 713-792-2933.

Attitudes Toward MEN1 Genetic Testing in Minors Survey

Instructions: We are interested in learning about your attitudes toward MEN1 genetic testing for healthy children who are under the age of 18. As you may know, the best age for healthy children to undergo MEN1 genetic testing is unknown due to several medical, social, and psychological reasons. We wish to learn about your experience and attitudes toward such testing.

Part 1: The following are questions about YOU.

1. What is your age: _____

2. What is your gender?

   ☐ Male ☐ Female

3. Where do you currently live? State: _____ Country:_____

4. What is your marital status?

   ☐ Single ☐ Married/Long Term Partner ☐ Separated ☐ Divorced ☐ Widowed

5. What is the highest grade or level of schooling you completed?

   ☐ Some high school
   ☐ High school graduate
   ☐ Some college
   ☐ College graduate (4 Year Degree)
   ☐ Associate's degree
   ☐ Upper-level degree

Please fill out this survey if you are the **SPOUSE OR PARTNER** of a person with MEN1 ID#

6. What is your current occupational status?

☐ Employed (Full Time) ☐ Homemaker
☐ Employed (Part Time) ☐ Student
☐ Unemployed (Not seeking a job) ☐ Retired
☐ Unemployed (Seeking a job)

7. What is your (combined) annual household income?

☐ Less than $25,000 ☐ $50,000 - $75,000
☐ $25,000 - $50,000 ☐ More than $75,000

8. Please check all of the following that apply to you:

☐ I am currently married to someone who has MEN1.
☐ I used to be married/partner to someone who has MEN but we are now separated.
☐ I have biological children who have MEN1, or who are at risk to inherit MEN1
☐ I have step children/adopted children who are at risk to inherit MEN1

9. How many members of your family or your spouse's/partner's family have been diagnosed with MEN1?

☐ None
☐ 1-2
☐ 3-4
☐ 5 or more

10. Do you or your spouse/partner have any relatives who have died from complications of MEN1?

Yes ☐ No ☐

If yes, how old were they when they died? _____

11. How severely do you feel MEN1 has affected your or your spouse's family's health and well-being? (Please circle a number on the scale below).

Not at all		Somewhat		Greatly
1	2	3	4	5

12. Has anyone in your family been diagnosed with an MEN1-related tumor before 18 years of age?

☐ Yes ☐ No If yes, how old were they? _____

If yes, how are they related to you (for example, sister, cousin, etc.)? _____

Part 2: The following questions are intended to find out what people know about cancer and genetic testing so that we can improve our educational efforts. This is not a test. We are simply interested in finding out what the general level of knowledge is regarding these topics. Please indicate whether you think each statement is true or false, or if you don't know.

13	An altered MEN1 susceptibility gene can be inherited from either parent.	True	False	Unsure
14	If Lisa looks more like her mother than her father, she has probably received more of her genetic information from her mother.	True	False	Unsure
15	A person who carries an altered MEN1 susceptibility gene will definitely develop features of MEN1 in his or her lifetime.	True	False	Unsure
16	Susan is the first born in her family. Her mother, who has MEN1, was also the first born. Thus, Susan has a higher risk of developing MEN1 than her younger brothers and sisters.	True	False	Unsure
17	Rick has had genetic testing for an MEN1 gene alteration that was found in his family. His results were negative; therefore, he is not at increased risk to develop features of MEN1.	True	False	Unsure
18	Kelly has had genetic testing for an MEN1 gene alteration that was found in her family. Her results were negative; therefore, her children are not at risk to inherit MEN1 from her.	True	False	Unsure
19	John's father has an altered MEN1 gene. The chance that John has inherited this gene alteration is 50% or 1 in 2.	True	False	Unsure
20	Once a gene alteration has been detected in a person with MEN1, their family members can be tested for the gene alteration to know for certain whether or not they also have MEN1.	True	False	Unsure

Part 3. Please think about your experience with MEN1 in your family. Please indicate how frequently each comment was true for you <u>during the past seven days.</u>

		Not at all	Rarely	Sometimes	Often
21	I thought about it when I didn't mean to.	1	2	3	4
22	I avoided letting myself get upset when I thought about it or was reminded of it.	1	2	3	4
23	I tried to remove it from my memory.	1	2	3	4
24	I had trouble falling asleep or staying asleep because of pictures or thoughts about it that came into my mind.	1	2	3	4
25	I had waves of strong feelings about it.	1	2	3	4
26	I had dreams about it.	1	2	3	4
27	I stayed away from reminders of it.	1	2	3	4
28	I felt as if it hadn't happened to me or it wasn't real.	1	2	3	4
29	I tried not to talk about it.	1	2	3	4
30	Pictures about it popped into my mind.	1	2	3	4
31	Other things kept making me think about it.	1	2	3	4
32	I was aware that I still had a lot of feelings about it, but I didn't deal with them.	1	2	3	4
33	I tried not to think about it.	1	2	3	4
34	Any reminder brought back feelings about it.	1	2	3	4
35	My feelings about it were kind of numb.	1	2	3	4

Part 4: The following questions ask about your personal feelings about genetic testing in healthy minors (in other words, individuals with no medical conditions who are younger than age 18). Please indicate your agreement with each of the following statements using the scale below.

		Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
36	Children under age 18 should be given the opportunity to be genetically tested for the MEN1gene alteration	1	2	3	4	5
37	Parents should decide if their children are allowed to have an MEN1 genetic test or not, even if a doctor disagrees	1	2	3	4	5
38	Even though some of the conditions associated with MEN1 may not affect people until they reach adulthood, children should still be offered MEN1 genetic testing	1	2	3	4	5
39	Children should be involved in making the decision about whether or not they have MEN1 genetic testing	1	2	3	4	5
40	I am in favor of MEN1 genetic testing for children	1	2	3	4	5
41	If children are tested and they turn out to carry an MEN1 gene alteration (that is, they test positive), they should be told about their test result immediately	1	2	3	4	5
42	Even if there is no known prevention for the conditions associated with MEN1, children should be offered MEN1 genetic testing	1	2	3	4	5

43	If children are tested and they turn out to carry a MEN1 gene alteration (that is, they test positive), then this information should be shared with the child's pediatrician	1	2	3	4	5
44	I want my child to have genetic testing for MEN1 before age 18	1	2	3	4	5
45	If children are tested and they turn out not to carry an MEN1 gene alteration (that is, they test negative), they should be told about their test result immediately	1	2	3	4	5
46	The benefits of children participating in MEN1 genetic testing outweigh the risks	1	2	3	4	5

Part 5: The following list includes reasons some people give for wanting or not wanting to have their child have genetic testing. Please indicate how important you feel each of the following is in making a decision to have MEN1 genetic testing for your child using the 1-5 point scale.

		Not Important	Slightly Important	Somewhat Important	Important	Very Important
47	I would be relieved to know my child did not have MEN1	1	2	3	4	5
48	My own experience with MEN1 makes me more concerned about my child's risk for the disease	1	2	3	4	5
49	I'm afraid I would get too upset	1	2	3	4	5
50	I / My child could plan for the future	1	2	3	4	5
51	I'm afraid my child would get too upset	1	2	3	4	5
52	I am concerned that having the test might cause problems with my child's insurance	1	2	3	4	5
53	I am concerned about my family's reactions	1	2	3	4	5
54	I want to learn whether my child is at risk for MEN1	1	2	3	4	5
55	I am worried about how it would affect my relationship with my child	1	2	3	4	5
56	I'm not sure if the genetic test is accurate	1	2	3	4	5
57	Something could be done to improve my child's health	1	2	3	4	5
58	I have a responsibility to let my child know if he/she has MEN1	1	2	3	4	5
59	I just want to know	1	2	3	4	5
60	The cost of genetic testing is too expensive for my family to afford	1	2	3	4	5

61. What do you feel is the ideal age for an individual to have MEN1 genetic testing? Why did you choose this age?

Please fill out this survey if you are the **SPOUSE OR PARTNER** of a person with MEN1 ID#

The following questions are optional:

Please indicate if we may contact you by phone with any follow up questions:

Yes No

Name: _____

Phone Number: _____

We would like to include as many people as possible in this survey. Individuals with MEN1 and their spouses/partners are eligible. Please tell us about any friends or relatives who may be interested in participating in our study:

Name: _____

Relationship to you: _____

Email: _____

Phone: _____

Address: _____

_____

_____

Name: _____

Relationship to you: _____

Email: _____

Phone: _____

Address: _____

_____

_____

Thank you very much for completing this questionnaire. The information you have provided has been very helpful and we appreciate your thoughtful answers.

APPENDIX D: REMINDER LETTER

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Clinical Cancer Genetics Program
T 713-563-1908 F 713-745-1921
Unit 444
1400 Hermann Pressler Dr
Houston, TX 77030-4008

Date

Name

Address

Dear Ms./Mr. <Name>:

Over the last several weeks we have tried to contact you at the above address about our study *Parental Attitudes of Predictive MEN1 Genetic Testing in Minors.* As of <*the date shown at the top of this letter*>, we have not received the questionnaire back from you nor have we received a refusal to take part in this study. It is possible that you may have sent in your survey and our records have not been updated yet. If you have already completed the survey, thank you for your response and please disregard this letter.

We are interested in obtaining information about parental attitudes toward MEN1 predictive genetic testing in their healthy children. The questions that you will be answering will help the researchers and physicians to better understand the needs of families with children at risk for MEN1 and provide the appropriate services. Participation in the study involves completing a questionnaire.

If you are interested in taking part in this study and have lost the questionnaire, we have enclosed another copy for your convenience. Patients who have been diagnosed with MEN1, please complete the white survey. Spouses or partners of persons with MEN1 please complete the yellow survey. We are interested in responses from both patients and spouses but responses will still be included even if only one person is available to participate. If you do not wish to take part in this study, please indicate this and also return the blank questionnaire to us in the pre-addressed envelope.

If you prefer the online survey, please go to http://www.surveymonkey.com/s/MEN1inminors and follow the instructions. You will need to enter your ID user number, which is <insert ID#>. The online survey consists of the same questions as the one that is included in this packet and was created using a professional account on Survey Monkey, which is a confidential survey making tool. Your response will be maintained strictly confidential and will only be shared with study staff.

Completion of this survey is optional and confidential. Due to the anonymous nature of the study, questionnaires will not be able to be withdrawn once they have been submitted. If you have any questions or would like more information please contact, the Clinical Cancer Genetics Program or your genetic counselor at (713) 745-7391 or e-mail ccg@mdanderson.org. Thank you very much for considering this invitation to participate in our study.

Sincerely,

Katie Rock, BA	Thereasa Rich, MS, CGC	Elizabeth Grubbs, MD
Genetic Counseling Intern	Genetic Counselor	Assistant Professor

APPENDIX E: OPEN ENDED SUREVEY RESPONSES

- I would say when they are reaching puberty or early teens. I feel that if it is done early on, i.e. infancy, then it would cause unnecessary heartache when it is important to be bonding with your child. I also think there is less risk at infancy and younger years of having complications due to MEN1. I feel at puberty the child is old enough to involve themselves in whether they want the testing and their maturity level would help them understand to some extent a very complicated diagnosis.
- Being a female, I began showing signs around the age of 13 or having female problems, also they may start to get the mole like spots on the face.
- 8-10
- 1. It could happen at any age. Very concern 2. There is no age of when humans get MEN1 it just develop in your system. By that time it mite be to late for processes
- It's a independent decision for each parent. I found out that I had MEN1, back in 1995 when I was 33. My daughter, at the time was 14. I stressed and worried over the fact that I could of passed the gene onto her. Not knowing was stressful. Finally, in 2003 we found out that genetic testing was available (here at MDAnderson) my daughter was 22 - We definitely wanted the testing. She was getting married and considering starting a family, she also wanted to know. Luckily, she was negative to carry for gene. If genetic testing was available to us back in 1995, we would choose to have her tested.
- Not sure, depends on maturity of child, but probably 12 or 13 years old. Old enough to understand ramifications/consequences.

- By age 10. So you can start monitoring the markers (calcium, Prolactin, PTH, gastrin, etc.) if tested positive.
- I feel a child should be tested as soon as doctor's are confident that results would be accurate. If there is any chance of change of testing I would have peace of mind in having a second testing done. I do not feel it is ever too early to be on the lookout for symptoms with MEN1. As negative result is best, at least with a positive result we can be more cautious with our children as they mature. Personally I have doubts as to where I would be now had I not have known about my condition only because of my family history.
- I was diagnosed at 34 after pancreatic cancer surgery. My father was diagnosed two years after me! My twins were very mature at age 14 and we talked about testing and what it might mean. They both wanted to be tested. They wanted to know the results whether good or bad. (obviously you would tell them if negative to celebrate and avoid anxiety.)

  I was devastated to find out my boys were positive. They are identical so we knew the chance that if one was positive, both likely would be.

  Since diagnosis, my boys have yearly screening and when one son had a blood sugar issue, we acted quickly to rule out a PNET.
- 16-18, Most young people, at this age, would have some level of maturity to understand what genetic testing is and why it might be important for them personally. They may have seen a grandparent, parent or sibling deal with the presentation of symptoms or surgery and testing could enhance their knowledge. By this age some could have had opportunity to study biology and all the new ways technology is

discovering more specific and accurate health data. Most would have completed puberty and have some stabilization of hormones.

- At any age that the child could understand what illness is. That things can go wrong with your body. That its not your fault.
- As a parent, I would like to know if son was + or - before puberty onset.
  While I realize that some individuals handle information differently, I would like to start a baseline for certain tests and choose an acceptable monitoring schedule through pediatrician or other dr. For kids, I do not think it would need to be as frequent as adults with manifestations. My MEN has been monitored/addressed proactively and as a result does not impact my life in a major or negative way. I hope the same for my son. Information allows one to plan…and if necessary anticipate. I prefer to have as much info as possible. I do not feel that a child (younger than 18) needs to know…unless the disease manifests itself in some way…and even then some concepts may be beyond their grasp. My opinion may shift if test results impacted insurance options now or in future.
- About age 25 when they are somewhat more mature and can make better decisions about their lives.
- 17. They should be old enough to handle the results and are still living at home.
- I wouldn't support the testing for children under 12, but 12-18 is appropriate.
  It's an individual choice. If family members exhibit symptoms, the testing may be more important.
- 13, they will be more understanding

- I don't feel the age of the test is as important as when the child is told/explained about the disease
- As soon as possible --> had my M EN1 been discovered earlier, it likely would have resulted in less-invasive surgery. The tumors could have been removed earlier and saved me a more healthy pancreas.
- 14 - old enough to understand the situation.
- 18 Knowledge is power. Knowledge can overcome fear.
- 14 years of age. They may be able to better understand the ramifications of MEN1 related medical problems.
- In my family, MEN1 has not been an issue until late teenage years (symptom wise). I feel during the child's teens would be a good time to test and explain to the child what it is. I don't see a sense in putting the stress into a child's life if there is no preventative care needed. Once the child knows MEN1 could be a factor in their health they should be tested. I felt more stress waiting for the test results than I have felt since knowing I have MEN1. In the end I would like my child to make that decision for herself and share my experience with her to help her decide.
- Not qualified to say. I feel it is important to know as soon as possible and educate all involved including medical professionals.
- 17 yrs old This is an age that a child can become more responsible and able to understand the diagnosis. The decision can be made in regards to family planning. This is also the age most of my family began to have symptoms of high calcium and kidney stones. Therefore, the diagnosis would have been made prior to symptoms and not be an

"elephant in the room." It is better to know than to have an unknown hanging over your head.

- 17 young enough to understand, but old enough to be able to handle the condition.
- Before the age of 10. My experience was that my hyper-parathyroidism was already present at age 11. It's also my opinion that if a child is diagnosed younger that they will accept MEN 1 and the resulting exams/testing as a 'normal' part of their life.
- I believe that the ideal age for someone to have genetic testing for MEN1 should be around 6-8 years old. I say that because that is about the time I started being a "sickly" child and went for years with no answers as to what was going on. I also believe that if they would have tested me for MEN syndrome when they found my first pituitary tumor and was on synthoid at the time. Basically, where I come from they have never heard of such and just kept giving me meds that didn't work and the problems were getting worse. I have to travel hours to Dallas or Houston to find someone to treat me because all of the local doctors just look at me and say that I have way too many problems and am way to complicated.
- Before 10 - Not Sure Really
- 13..so that as a young adult children can have the pros and cons carefully explained to them
- I am not sure there is a good age. Mine was detected by accident I will never know if all of the pain, anguish and worry has been for nothing. maybe I would have got though to old age with no problems. Instead I now live in fear. I have had 2 operations in the last 3 years but never had a single symptom. I rarely saw a doctor and thought I was fitter

than all of my peers leading a physically active lifestyle, never had a day off sick. I considered I was a particularly optimistic and strong person, I am now in receipt of councelling. It is known that stress affects the immune system- so is causing stress going to make the development of tumours more likely? This is a Kafkaresque world. I wouldn't want to put this onto any one else and certainly not a young person. Should an easy "cure" be forthcoming of course this changes everything.

- Would rather treat symptoms then worry about having the genetic mutation. If a family member is in a research trial that does the testing, then so be it. But once there is a positive in the family, I don't feel any other family member needs to be genetically tested. Again it is about treating the symptoms not the genetic test.
- 25. Ideal age to make informed decisions
- Age 10 because they are old enough to understand but young enough to process the information for a long time before signs/symptoms. Also, in the rare case the child may already need treatment at a young age.
- I am not sure what the ideal age would be.
- 21/22 Except in exceptional circumstances, once adult education is completed
- 5-10 years old. Tumors have been shown to develop this early, so in addition to psychological benefits of a negative test, one saves money on annual screenings. If positive, the risks for insurance, etc. seem outweighed. Also, they are old enough to learn about MEN.

- At birth. Less traumatic for the child (who wont remember having it), and gives parents options with regard to age to begin screening etc. I have heard that children as young as 5 have shown symptoms
- 10. It seems like a reasonable age for a child to begin to understand the implications of a genetic test and a genetic disorder.
- I think a child should be tested whenever their parents think, My son will be tested in the new year when he reaches 5, and my youngest may get tested before that age. My eldest is being tested when he turns 5 because it is the recommended age here in the UK, all of my family history has shown that we suffer with MEN 1 symptoms from an early age and I think my child has the right to know what may or may not happen in his life, if the test is positive he will be told when he can understand what it means and he can make the decisions about the screening. My mother died at the very very early age of 34 when her children were just 11 and 13, this impacts my decisions also because my sons both need to understand why their grandma isn't here and also why their mummy is sometimes in hospital. They deserve to know whether they have MEN regardless of age.
- I didnt have a choice at a younger age. the family was unaware of the condition. until my late 30s at which point I had suffered for years. I was tested positive at 40
- 10 years old
- 16 as i would want them to have the ability to make an informed decision and to be able to manage the concequences mentally and physically if necessary

- Ten years old is the age offered to children in Scotland. I feel this is young enough unless they show signs of the illness before this age, as they don't really understand what is going on. Emotionally it is very difficult for them too. My child had a positive diagnosis at the age of ten and has been quite unwell over the last two years from age 12 to 14. so for me, the genetic testing was important and it now means that my daughter is kept under medical supervision which puts our minds at ease. Admittedly though she has found the diagnosis difficult mainly because she has watched myself (her mum), struggle with the illness since she was little and doesn't want to go through what I am going though. It scares her about what the future may hold for her.
- As soon as MEN is known for a parent. It can help in how to approach healthcare. If there are tumors it is better to find them early.
- 16-
- I would say 15-18 is a good age, as before that you won't necessarily understand the condition and it's implications and you also have the emotional maturity to deal with it (though 15 - 18 can be a testing time anyway!) In addition I would also suggest that testing before 2 years of age is appropriate too as it means that having the condition is normal, so no emotional adjustment is needed (if that makes sense).
- From birth if there is already MEN1 in the family or ASAP if they show any signs
- 10. This is when I developed symptoms
- If insurance isn't a problem then as early as possible, there are cases of hyperparathyroidism developing in pre-school children, therefore I feel its important to start checking early as possible to avoid long term health problems.

- The age would depend on the individual's health and ability to understand the issues. If a child of a parent with MEN1 is unwell with symptoms that could be due to an MEN1 related tumour then this is an argument in favour of doing the test at that point, but if the child remains healthy, I would think it preferable to wait until the child is able to participate in such a decision. As children mature intellectually and emotionally differently, and their family circumstances differ, I think this should be decided on an individual basis with no prescribed age. In countries other than the UK, the issue of insurance difficulties would be a strong factor against testing both of minors and adults (health insurance is universal, free and very comprehensive in the UK - and the test itself is paid for by the national health service, so this is not a concern in the UK).
- 10, when the child can understand some of it, but before getting to be a teenager when it became more traumatic
- I would like to know as soon as a child is born. If the test is positive you can keep a close eye for any MEN1 symptoms as early as needed to keep the childs health as good as possible.
- 5 YEARS OLD, BECAUSE YOU CAN EXPLAIN TO THEM WHY THEY ARE HAVING THE TEST & FOR FUTURE MONITORING.
- Age 8, earlier the better. Enabling doctors with the information to treat her for all medical issues is critical
- 4. At age 4 the child's parents could make decisions about possible procedures before their child begins school.

- 10-12 From a developmental viewpoint since it affects the pituitary which can effect hormone levels etc which may or may not have developmental impact during teenage years

  25+ From insurance perspective - can be difficult to get insurance on own unless part of a group coverage. Maybe that has changed with new insurance laws

- With a child that started having trouble at 13 and always feeling that we were "behind the curve" on dealing with medical issues, I feel anywhere from 8-12 years of age is appropriate?

- 8-10years old, They can understand it more.

- If symptoms appear (kidney stones, thyroid, parathyroid, pituitary abnormalities) then I would encourage earlier gene testing. If symptom free (according to blood work) I would delay testing until after 18 or 21. Great concern is for health insurance and job hiring prejudice of having "preexisting condition."

  Also of great concern is the psychological effect at any age of having this diagnosis hanging like a black cloud, if some family member (like my daughter) had severe consequences- even if they came on after 40.

  Important to note:

  We did not learn of my husband's MEN1 until we were in our 60's. It would have made a difference in our family planning if we had learned of this in our 20s.

  Thank you. Glad to help in any way we can.

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