ATA Updated MTC Guidelines

By Carol Corbitt on Thursday, June 20, 2013 at 10:37 AM

http://thyroidguidelines.net/medullary/resultsb

- Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists
- American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer
- American Thyroid Association Design and Feasibility of a Prospective Randomized Controlled Trial of Prophylactic Central Lymph
- American Thyroid Association Statement on the Essential Elements of Interdisciplinary Communication of Perioperative Information
- Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpart
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- Radiation Safety in the Treatment of Patients with Thyroid Diseases by Radioiodine 131I: Practice Recommendations of the America
- Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer
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Results B [B] Initial diagnosis and therapy of preclinical disease in MEN 2 syndromes

MEN 2 is an autosomal dominant hereditary cancer syndrome that implies a 50% risk to offspring of a carrier to inherit the disorder. It is caused by missense mutations in the *RET* protooncogene, that result in ''gain of function'' (44). All three clinical subtypes of MEN 2 are characterized by the presence of MTC.

[B1] Clinical manifestations and syndromes of RET *mutations in MEN 2A (Table 5).* The most common clinical subtype of MEN 2 is type 2A. The typical age of onset of this condition is the third or fourth decade of life and is characterized by a triad of features: MTC, PHEO, and PHPT. Nearly 90% of gene carriers will develop MTC, but this is dependent upon the mutation (2). The risk of developing unilateral or bilateral PHEO is as high as 57%, and 15–30% of gene carriers will develop PHPT (2,40,45). In the vast majority of cases, MEN2A is caused by mutations affecting cysteine residues in codons 609, 611, 618, and 620 within exon 10 and, most commonly, codon 634 in exon 11 of *RET* (46).

Mutations in the *RET* codon 634 are causative of cutaneous lichen amyloidosis (CLA) in some MEN 2A/FMTC families (47).

Brauckhoff *et al.* (48) described papillary thyroid cancer in 9.1% of patients with *RET* mutations in exons 13 and 14, although this is considered a fortuitous association.

Germline mutations in *RET* have also been implicated in 10–40% of cases of Hirschsprung disease, with higher frequencies associated with familial cases (49,50). Hirschsprung disease is defined as the congenital absence of the enteric innervation, which causes bowel obstruction in infancy. In this disorder, deletions, insertions, missense, and nonsense mutations have been demonstrated throughout *RET*. These alterations cause loss of function, or inactivation of the encoded protein, and have reduced, sex-dependent penetrance and are associated with Hirschsprung disease without MEN 2A/FMTC. However, Mulligan *et al*. (51) found that Hirschsprung disease cosegregated with some activating mutations of MEN 2A/FMTC, although the penetrance is low. In all of these patients, the mutations occurred in exon 10 (Table 5) (51).

Table 5. Genotype–Phenotype Correlations and Risk Levels for Aggressive Medullary Thyroid Cancer

ATA risk MTC risk MEN 2Ad MEN

2Bd References Mutation Exon levela levelb FMTCc MTC PHPT PHEO CLA HSCR MTC PHEO G321Re 5 A + MA - - - - - - (100) 531/9 base pair duplication 8 A + MA - - - - - - (364) 532 duplicatione 8 A + ? - - - - - - (177) C515Se 8 A + MA - - - - - - (365) G533C 8 A + MA - R - - - - (99,366–368) R600Qe 10 A + MI - - - - - - (369) K603Ee 10 A + MI - - - - - - (370) Y606Ce 10 A + ? - - - - - - (371,372) C609F/R/G/S/Y 10 B 1 + MA MI R - + - - (14,46,85,373–375) C611R/G/F/S/W/Y 10 B 2 + MA MI R - + - - (46,85) C618R/G/F/S/Y 10 B 2 + MA MI MI - + - - (46,85) C620R/G/F/S/W/Y 10 B 2 + MA MI MI - + - - (46,85,374) C630R/F/S/Y 11 B + MA R R - - - - (73,376,377) D631Ye 11 B + ? - - - - - - (378) 633/9 base pair duplication 11 B + MA MI MI - - - - (379) C634R 11 C 2 - MA MI MA + - - - (46,85,380,381) C634G/F/S/W/Y 11 C 2 + MA MI MA + - - - (46,85,380–382) 634/12 base pair duplication 11 B + MA MI - - - - - (383) 635/insertion ELCR;T636P 11 A + MA - - - - - - (371) S649L 11 A + MI R - - - - - (14,124,384,385) K666Ee 11 A + MI/MA - MI - - - - (371) E768D 13 A 1 + MA R R - - - - (46,73,90,378) N777Se 13 A + MI - - - - - - (386) L790F 13 A 1 + MA R R/MI - - - - (86,378) Y791F 13 A 1 + MA MI MI - - - - (86,378,387) V804L 14 A 1 + MA MI R - - - - (46,86,388) V804M 14 A 1 + MA R R - - - - - (46,86,388,389) V804M+V778If 13/14 B + MA - - - - - - (390) V804M+E805K 14 D - - - - - - MA MA (71) V804M+Y806C 14 D - - - - - - MA MA (72–74) V804MþS904Cg 14/15 D - - MI - - - MA - (101) G819Ke 14 A + ? - - - - - - (14) R833Ce 14 A + ? - - - - - - (391) R844Qe 14 A + ? - - - - - - (14,378) R866We 15 A + MA - - - - - - (392) A883F 15 D 3 - - - - - - MA MA (393,394) S891A 15 A 1 + MA R R - - - - (14,395–397) R912P 16 A + MI - - - - - - (14,398) M918T 16 D - - - - - - MA MA (46)

aRisk from aggressive MTC: level D is highest risk. bRisk from aggressive MTC from the Seventh International Workshop on MEN (2): level 1, high risk; level 2, higher risk; level 3, highest risk. cPresence (+) of inherited MTC in the absence of PHPT or PHEO has been described, although the number of family members and number of family generations studied and duration of follow-up is variable. Historically, mutations initially considered diagnostic of FMTC have eventually demonstrated some penetrance of the MEN 2A phenotype. The absence (-) of association with FMTC indicates that inheritance of MTC in isolation is very unlikely. dOrgan-specific penetrance: MA, majority; MI, minority; R, rare. eMutations based on limited families=case reports and may represent variants of unknown significance. fPhenotype associated with corneal nerve thickening. gPhenotype associated with mucosal neurilemmomas. gPhenotype associated with mucosal neurilemmomas.

- **DEFINITION 1** MEN 2A is defined as the presence of MTC, PHEO, and PHPT associated with a germline *RET* mutation. There are rare families with classical features of MEN 2A in the absence of an identifiable *RET* mutation. In a patient with one or two of the clinical features of MEN 2A, the only way to be certain of a diagnosis of MEN 2A is to identify a *RET* mutation or identify the clinical features of MEN 2A in other first-degree relatives. In the absence of an autosomal dominant familial inheritance pattern or *RET* mutation, at least two of the classical clinical features of MEN 2A are required to make a clinical diagnosis of MEN 2A. In the presence of

a germline *RET* mutation and in the absence of any clinical features, that individual is said to be at risk for the clinical features of MEN 2A, and appropriate medical management should ensue.

[B2] Clinical manifestations and syndromes of RET mutations in FMTC. Defining and separating FMTC from MEN 2A has been challenging. The most rigid definition is multigenerational transmission of MTC in which no family member has PHEO or PHPT (26); a less rigid definition is the presence of MTC in four affected family members without other manifestations of MEN 2A (46). The controversy regarding this syndrome focuses on the concern that premature categorization of a family with a small number of MTC-affected individuals as FMTC could mask the eventual identification of a PHEO (52). The typical age of onset of this condition is later in life than in MEN 2A patients, and the penetrance of MTC is lower (53,54).
In the era of genetic testing, FMTC has been most commonly associated with mutations in codons 609, 611, 618, and 620 in exon 10; codon 768 in exon 13; and codon 804 in exon 14 (46). When FMTC is associated with mutations in codon 634 in exon 11, it is almost never C634R and is most commonly C634Y (46). Given the accumulating genotype–phenotype data over the last decades, and the eventual development of MEN 2A clinical features in some families once thought to have FMTC (52), FMTC is now viewed as a phenotypic variant of MEN 2A with decreased penetrance for PHEO and PHPT rather than a distinct entity.

- **DEFINITION 2** Familial MTC is a clinical variant of MEN2A in which MTC is the only manifestation. To prove that a particular kindred has FMTC it is necessary to demonstrate the absence of a PHEO or PHPT in two or more generations within a family or to have a RET mutation identified only in kindreds with FMTC (Table 5). In smaller kindreds or in those with a single affected generation, caution should be exercised in the classification of FMTC as there is the possibility of failure to recognize MEN 2A and the risk of PHEO.

[B3] Clinical manifestations and syndromes of RET mutations in MEN 2B. MEN 2B is the most rare and aggressive form of MEN 2 based on its development of MTC earlier in life (55–59). More than 50% of cases are *de novo* germline *RET* mutations (18,60). In multivariate analyses that incorporate disease stage and other factors, it has been suggested that the higher mortality rate of MEN 2B reflects its more advanced stage at presentation, rather than the tumor behavior once established (12,43,61,62). Like MEN 2A, MEN 2B is associated with PHEO. The youngest age at diagnosis of PHEO has been 12 years of age for the 918 *RET* mutation (63). In two series of MEN 2B patients, O'Riordain *et al.* (58) and Leboulleux *et al*. (64) reported median ages (range) at presentation of PHEO as 23 (13–32) and 28 (17–33) years, respectively. MEN 2B is distinguished from MEN 2A by the absence of PHPT and the presence of distinct developmental defects. These typical phenotypic features include musculoskeletal abnormalities (marfanoid habitus, pes cavus, pectus excavatum, hyponia, proximal muscle weakness); neuromas of the lips, anterolateral surface of the tongue, and conjunctiva; medullated corneal-nerve fibers; urinary ganglioneuromatosis and malformations; and ganglioneuromatosis of the intestine. Gastrointestinal manifestations including vomiting, dehydration, failure to thrive, and possible intestinal obstruction are often initial disease manifestations that present for medical attention (58,65–69). In one study of 21 MEN 2B patients, 90% had colonic disturbances, typically chronic constipation from birth (58). Megacolon developed in two thirds of patients, and about one third required colonic surgery. Brauckhoff *et al*. (70) reported that fewer than 20% of MEN 2B children manifested the typical MEN 2B phenotype during the first year of life, whereas 86%, 61%, and 46% demonstrated the inability to cry tears, constipation, or feeding problems, respectively. The average age of onset of MTC is 10 years earlier than seen inMEN 2A (2,55,63). The mutation M918T (exon 16) is present in >95% of patients with MEN 2B with 2–3% of patients harboring the A883F mutation in exon 15 (46). Rare patients with the MEN 2B phenotype have a double *RET* mutation (71–74) (Table 5).

- **DEFINITION 3** MEN 2B is defined as the presence of MTC, marfanoid habitus, medullated corneal nerve fibers, ganglioneuromatosis of the gut and oral mucosa, and PHEO associated with a germline *RET* mutation. There are rare families with classical features of MEN 2B in the absence of an identifiable *RET* mutation. In a patient with one or two of the clinical features of MEN 2B, the only way to be certain of a diagnosis of MEN 2B is to identify

a *RET* mutation or identify the clinical features of MEN 2B in other first-degree relatives. In the absence of an autosomal dominant familial inheritance pattern or *RET* mutation, the preponderance of the classical clinical feature of MEN 2B are required to make a clinical diagnosis of MEN 2B. In the presence of a germline *RET* mutation in a child, and in the absence of some or all of the clinical features, that individual is said to be at risk for developing the clinical features of MEN 2B, and appropriate medical management should ensue.

[B4] Role of germline RET testing in MTC patients (Figs. 1 and 2, Table 6). Germline testing of *RET* can be used to distinguish cases of sporadic from hereditary MTC (Fig. 2), and the precise *RET* mutations may suggest a predilection toward a particular phenotype (Table 5) and clinical course. This is important because the patient may also require surveillance and management of PHEO and PHPT, and additional family members may be at risk for developing MTC. Knowledge of the *RET* mutation can guide decisions regarding prophylactic thyroidectomy (Table 6) and intra-operative management of the parathyroid glands. Approximately 95% of patients with MEN 2A and MEN2B, and 88% of those with FMTC will have an identifiable *RET* mutation (2). In addition, about 1–7% of apparently sporadic cases have identifiable *RET* mutations (75,76), including about 2–9% with *de novo* germline mutations (19,77). *RET* mutations are more likely to be identified in patients with multifocal disease and/or MTC at a young age.

Table 6. American Thyroid Association Risk Level and Prophylactic Thyroidectomy Testing and Therapy

ATA risk level Age of RET testing Age of required first US Age of required first serum Ct Age of prophylactic surgery D ASAP and within the 1st year of life ASAP and within the 1st year of life 6 months, if surgery not already done ASAP and within the 1st year of life C <3–5 years >3–5 years >3–5 years Before age 5 years B <3–5 years >3–5 years >3–5 years Consider surgery before age 5. May delay surgery beyond age 5 years if stringent criteria are met.a A <3–5 years >3–5 years >3–5 years May delay surgery beyond age 5 years if stringent criteria are met.a aA normal annual basal ± stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference. ASAP, as soon as possible.

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- **RECOMMENDATION 1** All patients with a personal medical history of primary C cell hyperplasia, MTC, or MEN 2 should be offered germline *RET* testing. Grade: A Recommendation
- **RECOMMENDATION 2** The differential diagnosis in patients with intestinal ganglioneuromatosis should include MEN 2B, which together with their history and physical examinations, family history, and ganglioneuromatosis histology may prompt germline *RET* testing. Grade: B Recommendation
- **RECOMMENDATION 3** All people with a family history consistent with MEN 2 or FMTC, and at risk for autosomal dominant inheritance of the syndrome, should be offered *RET* testing. For MEN 2B this should be done shortly after birth. For MEN 2A and FMTC this should be done before 5 years of age (Table 6). Grade: A Recommendation
- **RECOMMENDATION 4** Lichen planus amyloidosis or pruritis in the central upper back may indicate the presence of a 634 codon mutation and should prompt genetic testing. Grade: C Recommendation
- **RECOMMENDATION 5** Pre- and post-test genetics counseling by a genetics counselor, or other qualified professional, should be offered to all patients undergoing *RET* testing. Grade: C Recommendation

[B5] Prophylactic thyroidectomy (When should it be performed in a clinically asymptomatic individual with documented RET mutation but a normal thyroid physical examination and no suspicious lymph nodes or thyroid nodules >5mm on US (if obtained)? See Fig. 1 and Table 6). MEN 2 patients who present with palpable MTC have a low rate of cure (78,79). In MEN 2 patients, biochemical surveillance to detect CCH or early MTC significantly increased the rate of surgical cure (79), yet sensitivity and specificity were imperfect because some individuals who had surgery did not

harbor *RET* mutations, while others experienced MTC recurrence (59,78). Unfortunately, in one series of MEN 2A or FMTC children who underwent prophylactic thyroidectomy at age 4 years or later, 11% experienced biochemical persistence or recurrence, all of whom were operated at age 13 years or later (80). Similarly, there was no persistent or recurrent MTC in a series of 50 children when they underwent prophylactic thyroidectomy and central neck dissection before age 8 years (81). Six children had persistent or recurrent disease postoperatively and had undergone surgery at ages 8, 10, 11, 14, 16, and 19 years old with *RET* mutations in codons 634, 620, 618, 620, 634, and 618, respectively. Of these children, four had no evidence of lymph node metastases at the primary surgery. Conversely, of the three patients with lymph node metastases at surgery, only one remained biochemically free of disease. Thus, biochemical surveillance for MTC has largely been replaced by the use of *RET* mutation status and knowledge of the age and penetrance of MTC in the codon mutated to guide the timing of prophylactic thyroidectomy (2,82,83). Unfortunately, metastatic MTC is not universally preventable in all MEN 2B patients despite prophylactic thyroidectomy shortly after birth (67).

At the Seventh International Workshop on MEN, a classification system was created for *RET* mutations based on risk for aggressive MTC (2). The purpose of the classification system was to offer recommendations for age of prophylactic thyroidectomy, predict phenotype, and establish who should be screened for PHEO (2). This system has been important, but may be improved by recognizing the more aggressive course of the 634 mutation, with young age of onset and a higher rate of PHPT and PHEO (15,84,85). Additionally, some *RET* mutations were not categorized by that system (including codon 630), or were judged appropriate to be reclassified based on more recent data (e.g. codon 609) (63). For these reasons, we have created a categorization system that makes these changes, and allows for periodic updating (see Table 5). ATA level D (ATA-D) mutations carry the highest risk for MTC. These mutations include codons 883 and 918, and are associated with the youngest age of onset and highest risk of metastases and disease specific mortality. ATA level C (ATA-C) mutations carry a lower, yet still high risk of aggressive MTC and include mutations at codon 634. ATA level B (ATA-B) mutations carry a lower risk for aggressive MTC mutations and include mutations at *RET* codons 609, 611, 618, 620, and 630. ATA level A (ATA-A) mutations carry the ''least high'' risk. Compared to ATA-B mutation carriers of the same age, these patients have lower serum Ct levels, lower tumor stage, and a higher rate of biochemical cure when they undergo prophylactic thyroidectomy at age ≥ 4 years old (80). ATA-A mutations include *RET* gene mutations at codons 768, 790, 791, 804, and 891. Despite this ATA categorization into four levels (A–D), differences in the development and behavior of MTC and the development of MEN 2A features are present between various *RET* mutations even within the same ATA level (86).

With the possible exception of certain ''least high risk'' ATA-A *RET* mutations, patients with germline *RET* mutations require prophylactic thyroidectomy (Table 6). At the MEN97 Workshop it was determined that surgery should be performed based on the results of *RET* testing for individuals with MEN 2 (87), as *RET* testing has a lower rate of false negatives and false positives than Ct testing (88), which was previously used for early identification and treatment of MTC (2). ATA levels B–D *RET* mutations are associated with nearly complete penetrance of the MTC phenotype at young ages and once metastatic are associated with a low rate of cure (81), and high rate of morbidity and eventual mortality. Early detection and intervention of MTC has been shown to significantly alter the associated mortality (2,79–81). Thus, the main debate now is the timing of prophylactic thyroidectomy during childhood, rather than if it should be done or not. ATA-A *RET* mutations comprise a group of phenotypes that are typically characterized by later onset of MTC that is associated with less aggressive clinical behavior. However, the phenotype of these *RET* mutations is heterogeneous within and between the various *RET* mutations so that at one end of the spectrum, and composing the majority, are MTC phenotypes with late onset, incomplete penetrance, and rare MTC related death (89,90). At the other end of the spectrum, are the unpredictable minority that have demonstrated aggressive MTC, as witnessed in a 6-year-old child with metastatic MTC with an 804 *RET* mutation (84,91). Proposed strategies to determine the timing of prophylactic thyroidectomy for *RET* mutations have included age cut-offs based on the youngest child reported in the literature with metastatic disease, the more typical age of MTC development for the genotype, basal ± stimulated* serum Ct measurements, annual neck ultrasound (US), the age that MTC developed in family members, and combinations of these factors (2,79,84,93). The incentive for early prophylactic thyroidectomy is to intervene before the development of metastases because once metastatic, these patients are often incurable (81,94). Further, thyroidectomy prior to lymph node metastasis obviates the need for central compartment lymph dissection which is associated with a higher rate of

hypoparathyroidism (81) and vocal cord paralysis. The incentive to delay prophylactic thyroidectomy is to optimize patient safety by operating on older children, whose surgery is technically less difficult and in whom treatment of iatrogenic hypoparathyroidism may be easier. Children undergoing thyroidectomy or parathyroidectomy have higher complication rates than adults, and have better outcomes when operated on by high-volume surgeons (95). There is also some benefit to delayed iatrogenic hypothyroidism (80). From a technical standpoint regarding preservation of parathyroid function, and a developmental standpoint regarding iatrogenic hypothyroidism, experienced surgeons report little benefit to delaying thyroidectomy beyond 3–5 years of life.

- **RECOMMENDATION 6** Infants with ATA-D mutations (MEN 2B) should undergo prophylactic total thyroidectomy as soon as possible and within the first year of life in an experienced tertiary care setting. Grade: B Recommendation
- **RECOMMENDATION 7** Children with ATA-C mutations (codon 634) should undergo prophylactic total thyroidectomy before they are 5 years old in an experienced tertiary care setting. Grade: A Recommendation
- **RECOMMENDATION 8** In patients with ATA-A and ATA-B *RET* mutations, prophylactic total thyroidectomy may be delayed beyond age 5 years in the setting of a normal annual basal ± stimulated* serum Ct, normal annual neck US, less aggressive MTC family history, and family preference. Surgery is indicated if all of these features are not present. For higher risk mutations (ATA-B), consider treatment before age 5 years in an experienced tertiary care setting, regardless of other factors. Grade: B Recommendation

[B6] RET *testing in asymptomatic people (In clinically asymptomatic people with normal thyroid physical examinations, who should undergo* RET *testing and why?).* Ideally, the initial individual to undergo *RET* testing in any family would be an affected individual with features of MEN 2. Once a germline *RET* mutation has been identified in a family, genetic counseling and *RET* mutation analysis should be offered to all first degree relatives (96,97). Offspring of a *RET* mutation–affected individual have a 50% risk of inheriting the mutation. Additional risks to members of the kindred are dependent on the relation to a known mutation carrier. Because the absence or presence of the family's mutation in a relative is so important to their future care, some experts advocate that the test be repeated to confirm the result. In the absence of affected individuals available for testing (due to death or other barriers) within an affected kindred to determinate the presence of a causative *RET* mutation, testing can be offered to unaffected individuals; however, the limitations of such testing need to be carefully discussed with the individual to be tested.

- **RECOMMENDATION 9** Once a germline *RET* mutation has been identified in a family, *RET* mutation analysis should be offered to all first degree relatives of known mutation carriers which should be done before the age of recommended prophylactic thyroidectomy whenever possible. Grade: A Recommendation

Additionally, testing of exon 10 should be considered in individuals with Hirschsprung disease (46). Although mutations are distributed throughout the gene, and some prefer sequencing of all exons in this setting, the most important clinical decision for Hirschsprung disease is whether they also have an activating exon 10 mutation which would confer risk of MEN 2.

- **RECOMMENDATION 10** Testing of exon 10 for activating *RET* mutations should be considered in individuals with Hirschprung disease. Grade: A Recommendation

[B7] RET *testing methodologies (Is all* RET *testing the same? How is this testing optimally done?).* A review of the laboratories listed in the GeneTests directory identifies 38 laboratories that are currently performing DNA analysis of *RET* for MEN 2A, MEN 2B, and familial or sporadic MTC (98). All of the laboratories listed use direct sequence analysis for mutation identification with or without the addition of target mutation analysis for selected hotspots. Although their approaches differ slightly, nearly all evaluate patients for mutations in the five most commonly mutated codons in exons 10 and 11 (C634R, C609, C611, C618, and C620) (46). Multiple laboratories additionally sequence exons 13, 14, 15, and/or 16, while only a few include exon 8. Typically, the cost of the analysis increases as more exons are sequenced. A

few laboratories sequence the entire coding region of *RET*, but at a substantially higher cost, and this is likely to be more testing than most patients require. Some laboratories (98) use a two-tiered approach to the analysis, starting with sequence analysis of the most commonly mutated ''hotspot'' exons and, at the request of the ordering physician, sequencing the remaining exons of *RET* if the initial analysis is negative (99,100). Tiered approaches are at risk of failing to detect rare double mutations. For example, there are a few reports suggesting that codon 804 mutations in conjunction with a second variant in *RET* could be associated with MEN 2B (71–73,101). Unfortunately, the phenotype is not particularly well documented in these reports.

- **RECOMMENDATION 11** Analysis of the MEN 2–specific exons of *RET* is the recommended method of initial testing in either a single or multi-tiered approach. Grade: A Recommendation
- **RECOMMENDATION 12** Sequencing the entire coding region of *RET* to identify MTC causative mutations is not recommended as the initial testing method (Grade: E Recommendation). However, it should be done when the analysis using the recommended method is negative in the clinical setting of MEN 2 or when there is a discrepancy between the genotype and phenotype. Grade: B Recommendation
- **RECOMMENDATION 13** Testing of patients with MEN 2B should include analyses to detect the M918T (exon 16) and A883F mutations (exon 15) present in virtually all of these patients. Grade: A Recommendation
- **RECOMMENDATION 14** In the clinical setting of MEN 2B and negative testing for M918T and A883F mutations, sequencing the entire coding region of *RET* should be performed. Grade: B Recommendation
- **RECOMMENDATION 15** Until the phenotype of MEN 2B associated with codon 804 mutations in conjunction with a second variant in *RET* is clarified, these patients and mutation carriers should be treated similarly to those with the more typical MEN 2B *RET*-causing mutations. Grade: C Recommendation

[B8] Genetic testing: privacy vs. notification of potentially affected family members. In a physician–patient relationship the duty to warn third parties of risk has been established in the case of *Tarasoff et al. v Regents of the University of California*, defined as the ''duty to act to prevent foreseeable harm'' (102,102a). However, as of 2006, only three legal cases regarding disclosure of genetic information have been brought to trial, two of which are specific to testing for cancer predisposition syndromes that take into account the duty to warn as well as the right to confidentiality (102a,103–105). The case of *Pate v Threlkel* (104), a case assessing duty to warn in an instance of FMTC tried in New Jersey, determined that ''a physician can fulfill the duty to warn by notifying the patient of the risk the disorder poses to family members with the patient expected to pass the warning, and to require the physician to seek out at risk relatives would place too heavy a burden upon the physician.'' However, in *Safer v the Estate of Pack* (105), a case assessing duty to warn in a family with familial polyposis syndrome, it was ruled that there was ''no impediment, legal or otherwise, to recognizing a physician's duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition. In terms of foreseeability especially, there is no essential difference between the type of genetic threat at issue here and the menace of infection, contagion, or a threat of physical harm.'' Thus, the law appears to have taken divergent views on the issue in these two cases under the two different jurisdictions.

Current accepted standards of clinical practice, existing as established professional guidelines, are extremely varied and provide room for interpretation with each case. These guidelines range from prohibiting direct communication between a patient's physician and their relatives, to allowing contact under special considerations regardless of patient consent. The American Medical Association and American Society of Clinical Oncology guidelines take into consideration the belief that the confidentiality of genetic testing is an absolute with no exceptions, and that the duty to warn at-risk relatives falls to the moral obligation of the patient, owing to the belief that the physician's foremost obligation is to the patient directly (106,107). However, many guidelines do allow for disclosure of results to at-risk individuals without the patient's consent, particularly when efforts to obtain consent have failed; when the information disclosed will prevent serious harm; when there is no other reasonable alternative to preventing harm; and precautions are made to only disclose the appropriate information. The World Health Organization, the American Society of Human Genetics, and the National Human Genome Research Institute, as well as many other national and international groups, have adopted this view (108). Probably superseding all of these opinions, guidelines, and case law are the Health Insurance Portability and

Accountability Act privacy regulations that make few exceptions for disclosure to inform or warn family members of genetic risk (109–111).

- **RECOMMENDATION 16** The duty to warn should be fulfilled by notifying a competent patient (or legal guardian) of the risk the inherited RET mutation may pose to family members, ideally in the setting of formal genetic counseling. This notification should include the seriousness of the disease and available forms of treatment and prevention. The highest recommendation should be made that the patient pass this warning to potentially affected family members, and the opportunity for genetic counseling and testing of these individuals should be provided. Conversely, physicians should not disclose confidential genetic or medical information without the patient's permission. When a patient or family refuses to notify relatives of their risk or to provide testing or treatment to legal dependents, the physician may involve the local medical ethics committee and or legal system. Grade: C Recommendation

[B9] Reproductive options of RET *mutation carriers.* Both preimplantation and prenatal testing are available to individuals with MEN 2 (112–115). These testing options rely on identification of the familial *RET* mutation prior to fetal or embryonic testing. Prenatal testing can be performed in the first or second trimester via chorionic villus sampling or amniocentesis, respectively. Preimplantation genetic diagnosis (PGD) is an *in vitro* fertilization technique that isolates and tests a single embryonic cell for single-site *RET* testing. The unaffected embryos are then transferred to the uterus. Therefore, PGD has the potential to remove the disease from the family as only embryos without a *RET* mutation are implanted.

The role of PGD in adult-onset disease remains controversial; it is generally offered for syndromes that have a young age of onset with significant cancer risk and associated morbidity or mortality. With an average age of onset under 30 years of age for ATA level B–D mutations (63) (and cases of metastatic MTC reported in the first months of life in MEN 2B), and a >90% lifetime risk for MTC and up to 57% risk for PHEO, PGD may be an option for individuals with MEN 2 and a known *RET* mutation (114,115).

While a couple may not wish to proceed with prenatal or preimplantation diagnosis, the clinician may have a ''duty to warn'' and at the minimum, notify the couple that these options are available should they be interested, according to the case of *Meier v Malloy* (103,115).

- **RECOMMENDATION 17** All *RET* mutation carriers of childbearing age should be considered for counseling about the options of prenatal or preimplantation diagnostic testing. Grade: C Recommendation

[*B10] Possibility of inherited disease in RET mutation–negative MTC patients and families (How should RET-negative MTC patients families be advised about the possibility of inherited disease?).* Patients with sporadic MTC tend to have unifocal disease, later age of onset, and absence of CCH (116–121). The probability that an individual with an apparent sporadic MTC will be found to have a *RET* mutation is about 1–7% (2,75,76,122–124). If one assumes a probability of ≤7%, and a detection of RET mutations in 95% of MEN 2A and 2B individuals and 88% in FMTC individuals, then the remaining risk of a patient with apparently sporadic MTC still actually having hereditable MTC despite no RET mutation being identified is <1% [prior probability x (1 -mutation detection frequency)] (2). Thus, additional testing of the patient or family for the development of MEN 2 features is not necessary. Conversely, in the rare family meeting clinical criteria for MEN 2A or 2B, or FMTC in the absence of a RET mutation, first-degree relatives of an affected individual have a 50% risk for inheriting the familial syndrome

- **RECOMMENDATION 18** In a family meeting clinical criteria for MEN 2A or 2B, or FMTC despite negative sequencing of the entire region of the RET oncogene, at-risk relatives should be periodically screened for MTC (neck US, basal ±stimulated* Ct measurement) and associated PHPT (albumin-corrected calcium or ionized calcium) and or PHEO (plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines) as indicated by the family phenotype. Screening should continue at 1–3 year intervals at least

until the age of 50 years or 20 years beyond the oldest age of initial diagnosis in the family, whichever is latest. Grade: C Recommendation

[B11] Preoperative testing of asymptomatic RET *mutation– positive patients for MTC, PHPT, and PHEO.* In clinically asymptomatic patients with a normal thyroid physical examination and documented *RET* mutation (Fig. 1), what are the roles of preoperative testing for MTC (Ct and cervical US, Table 6), PHPT, and PHEO? In such patients, the primary issues influencing their clinical care are the likelihood they have metastatic MTC, PHPT, and/or PHEO. The risk of metastatic MTC in the youngest MEN 2A children undergoing prophylactic thyroidectomy under age 5 years is very low(84),while there are less data regarding MEN 2B children operated at less than 1 year of age (55,58,67–70,96,125,126). Thus, the value of Ct or US testing in MEN 2A and FMTC children under age 5 years has not been established. Alternatively, of the published MEN 2B cases that include postoperative data, about half of the children operated by 1 year of life have demonstrated persistent disease. Unruh *et al*. (67) described a 9-week-old MEN 2B child with a preoperative Ct of 1150.9 pg/mL. The child was treated with a total thyroidectomy, which demonstrated CCH and microcarcinoma, and excision of three central nodes (apparently benign). Two months postoperatively the serum Ct was 14.1 pg/mL. Nine months later the Ct was 18.7ng/mL and bilateral neck dissection showed 39 benign lymph nodes and a postoperative Ct of 31.1 ng/mL. This case demonstrates several issues in the youngest MEN 2B patients: 1) post-natal ''prophylactic'' thyroidectomy to prevent metastatic disease is not possible in all patients, 2) a potential benefit to prophylactic lymph node dissection has not been demonstrated, and 3) the role of the preoperative Ct level in these children is not established. The influence of age on serum Ct is discussed below under the heading *Effects of age or sex on the normal Ct range*.

- **RECOMMENDATION 19** Children with MEN 2A or FMTC who are to undergo prophylactic thyroidectomy before 5 years of age may undergo preoperative Ct and cervical US assessment when >3 years old, whereas children older than 5 years require them because of the possibility of metastatic MTC, which would change their clinical management. Caution should be used in interpreting Ct values in children less than 3 years old, and especially in those during the first 6 months of life. Grade: B Recommendation
- **RECOMMENDATION 20** Children with MEN 2B who are to undergo prophylactic thyroidectomy before age 6 months may undergo preoperative Ct assessment, whereas older children require it. Cervical US should be done in MEN 2B children as soon as possible. These tests are recommended because of the possibilities of metastatic MTC and of test results changing clinical management. Caution should be used in interpreting Ct values in children <3 years old, and especially those in the first 6 months of life. Grade: B Recommendation
- **RECOMMENDATION 21** When it is decided to delay prophylactic thyroidectomy beyond the first 5 years of life in children with MEN 2A/FMTC:

  A. Basal serum Ct testing and cervical US should be performed annually starting by 5 years of age. Grade: B Recommendation B. The role of annual Ct stimulation* testing in these patients is less certain but may be performed. Grade: C Recommendation

Childhood PHEO (127–129) is rare in MEN 2. The vast majority of MEN 2 PHEOs are intra-adrenal and benign (63). PHEO has been reported at 12 years of age for both the 918 and 634 *RET* mutations (59,63). However, PHEO has occurred in younger children; 8 and 10 years old with 634 *RET* mutations (JF Moley and RF Gagel, respectively, personal communications, February 9, 2009). Of the ATA-B mutations, including the 609 mutation, the youngest have been 19 years old (85), while the youngest ATA-A mutation has been age 28 years (63). From a series of 206 RET mutation carriers, Machens *et al.* (63) reported that the 5th percentile for age of PHEO diagnosis in those with *RET* mutations was in the third and fourth decades of life, depending on the mutation (63). They concluded that annual screening for PHEO may be warranted from age 10 years in carriers of *RET* mutations in codons 918, 634, and 630, and from age 20 years in the remainder. Data suggest that measurement of plasma or urinary fractionated metanephrines is the most accurate screening approach for PHEO (130). There is a lack of consensus with respect to imaging the abdomen periodically for PHEO in the absence of abnormal metabolic screening (2).

- **RECOMMENDATION 22** Screening abdominal imaging for PHEO is not recommended in the absence of symptoms or biochemical data suggesting the tumor, except for the rare urgent need to exclude PHEO. Grade: D Recommendation
- **RECOMMENDATION 23** Symptoms or signs consistent with catecholamine excess, or an adrenal mass, should prompt biochemical testing for a PHEO. Grade: B Recommendation
- **RECOMMENDATION 24** In the absence of symptoms or an adrenal mass to suggest the possibility of PHEO, surveillance (including preoperative testing) should include annual plasma free metanephrines and normetanephrines, or 24-hour urine collection for metanephrines and normetanephrines beginning by age 8 years in carriers of *RET* mutations associated with MEN 2B and in codons 630 and 634, and by age 20 years in carriers of other MEN 2A *RET* mutations. Patients with *RET* mutations associated only with FMTC (Table 5) should be screened at least periodically from the age of 20 years. Grades: B Recommendation for genotype–phenotype distinctions, and C Recommendation for the frequency of testing.
- **RECOMMENDATION 25** Because of the high risk to the fetus and mother, women with a *RET* mutation associated with MEN 2 should be biochemically screened for PHEO prior to a planned pregnancy or as soon as possible during an unplanned pregnancy. Grade: B Recommendation

Childhood PHPT (131–134) is rare in MEN 2. In two large studies of MEN 2A patients affected by PHPT the median age at diagnosis was 38 years (133,134). Skinner *et al.* (59) reported children 13 and 18 years of age with PHPT from a series of 38 MEN 2A children.

- **RECOMMENDATION 26** Surveillance for PHPT should include annual albumincorrected calcium or ionized serum calcium measurements (with or without serum intact-parathyroid hormone [PTH]) beginning by age 8 years in carriers of *RET* mutations in codons 630 and 634, and by age 20 years in carriers of other MEN 2A RET mutations, and periodically with *RET* mutations associated only with FMTC (Table 5) starting from age 20 years. Grades: B Recommendation for genotype– phenotype distinctions, and C Recommendation for the frequency of testing.

[B12] Sources of Ct assay interference. Accurate and consistent measurements of serum Ct levels are of critical importance for the evaluation and long-term follow-up of patients with MTC. Over the past decade, commercial assay methods for Ct have progressed to the newest two-site, two-step chemiluminescent immunometric assays (ICMAs) that are highly specific for monomeric Ct. With two-site Ct-ICMAs, cross-reactivity or change in results due to procalcitonin; related peptides; hyperparathyroidism (135); pregnancy or lactation (136–138); inflammation, infection, or sepsis (139–141); bilirubin; hemolysis or hemoglobin; and lipemia all appear to be minimal (142–144).
Mild elevations in basal and pentagastrin-stimulated Ct levels may occur with CCH (145), autoimmune thyroiditis (146,147), chronic renal failure (142,148,149), and mastocytosis (150–153). Compared to the Ct assay upper normal value, these elevations are often up to a few fold higher, but occasionally be more than 10-fold higher (148). Minimal changes in serum Ct occur in healthy subjects with hypergastrinemia (154). The ''hook effect'' is less likely to occur with the two-site monoclonal, two-step assays, but should remain a concern in the interpretation of ''low'' Ct levels in patients with widely disseminated disease (155). Heterophilic antibodies (human antibodies that bind animal antibodies) have been described to cause falsely elevated (and rarely falsely lower) Ct levels (156–158). Nonthyroidal neuroendocrine tumors secreting Ct have been described including the foregut (159), pancreatic tumors (160,161), insulinoma (162), glucagonoma (163), VIPoma (164,165), carcinoid (166), prostate (167), small cell lung cancer (159), and large cell lung cancer with neuroendocrine differentiation (168). Two caveats which may be helpful diagnostically are that these tumors typically do not increase their Ct secretion in response to Ct stimulation testing and they usually produce less Ct per gram of tissue than is typical for MTC.

- **RECOMMENDATION 27** It should be recognized that minimal or mild elevations in serum Ct may be seen in multiple clinical settings including CCH, renal failure, and autoimmune thyroiditis. Elevated Ct levels may occur from

nonthyroidal neuroendocrine neoplasms and heterophilic antibodies. Falsely low Ct levels may occur in the setting of heterophilic antibodies and the ''hook effect.'' Grade: B Recommendation

[B13] Effects of age or sex on the normal Ct range. Considerable variability among commercial assay results (142) indicates a need to follow individual patients with the same assay over time. Laboratories should report the assay being used and notify clinicians of changes in methodology when they occur. If the method changes, optimally, Ct levels should be measured using both the current and prior methods to allow for a ''re-baselining'' of values. Conversely, if an unexplained change occurs in the Ct levels in a patient, a change in laboratory method should be considered as a potential cause. Current reference ranges vary with sex and are higher in men than women (142,144,169), possibly due to more C cells in men than women (170). Weak correlations between the Ct level and age, body mass index, and smoking have been reported (142). Depending on the assay used, about 56– 88% of normal subjects have serum Ct levels below the assay functional sensitivity, while 3–10% of subjects have Ct levels >10 pg/mL (142). Using the Advantage system (Nichols Institute Diagnostics, San Juan Capistrano, CA), Basuyau *et al*. (144) found the 95th percentile to be 5.2 ng/L and 11.7 ng/L in women and men, respectively. Limited data have suggested that serum Ct levels may increase in response to a meal, although other studies have found no impact (171–175).

- **RECOMMENDATION 28** Optimally, an individual should be followed using the same Ct assay over time. Whenever possible, a blood sample should be measured using both assays to reestablish the baseline when it is necessary to change the assay. Grade: C Recommendation
- **RECOMMENDATION 29** Laboratories should report the Ct assay being used, and notify clinicians of changes in methodology when they occur. Grade: C Recommendation
- **RECOMMENDATION 30** In the setting of an intact thyroid gland, Ct values should be interpreted in the setting of sex-specific reference ranges, at least in adults. Grade: B Recommendation

Few data exist on age-specific Ct levels for young children. Previous studies have suggested that Ct concentrations are particularly high during the first week of life, in low-birthweight children, and in premature infants (144). A previous two-site immunometric assay, that is no longer available, reported no difference in the mean Ct value for children (1.3 ± 2.7 pg/mL) and adults (0.9 ± 2.5 pg/mL) with more than half of the children having Ct levels <0.2 pg/mL with this assay (143). No significant sex difference was observed (143).
However, only a limited number of samples from children <3 years of age have been analyzed using a contemporary two-site immunometric assay. Using the Advantage system (Nichols Institute Diagnostics), Basuyau *et al*. (144) proposed a reference range of <40 ng/L in children under 6 months of age and <15 ng/L in children between 6 months and 3 years of age, and indicated that in children over 3 years of age the values were indistinguishable from those observed in adults. The highest value observed in their series was 75 ng/L at age 4.5 months with a follow-up value of 32.4 ng/L one month later (144).

- **RECOMMENDATION 31** Due to the limited data available on the normal range for serum Ct in children <3 years of age and the probability that it may be higher than in adults, caution should be used in interpreting these values in young children. Grade: B Recommendation

[B14] Surgery for the youngest MEN 2B patients (Fig. 1). The youngest MEN 2B patients are <1 year of age. The age of MTC onset is much earlier in MEN 2B than in MEN 2A and FMTC (60,63). Foci of MTC may be present in infancy and nodal metastases can become apparent in early childhood (59,60,64,65,67,78). For these reasons, it is recommended that genetic testing be done as soon as possible after birth in at-risk infants (Table 6), and that thyroidectomy be performed in MEN 2B *RET*-positive individuals as soon as possible and within the first year of life if possible (Table 6, Fig. 1). It should be noted, however, that this opportunity is uncommon given the rarity of MEN 2B and that more than 50% of cases are *de novo* germline *RET* mutations diagnosed much later in life (18,60). Children undergoing thyroid or parathyroid surgery have higher complication rates than adult patients that are minimized when surgeries are

performed by high volume surgeons (95). This emphasizes that it is important that the surgeon operating on infants be experienced, and familiar with the recurrent laryngeal nerve and parathyroid gland management in young children. The parathyroid glands are very small and translucent in infants. Proper identification and handling is critical to avoiding hypoparathyroidism. Nodal metastases may already be present, and a thorough central neck dissection may require removal and autotransplantation of parathyroid glands, a technique in which the surgeon should have expertise. While an elevated Ct level may indicate the presence of MTC, and high levels are consistent with metastases (94), the role, interpretation, and value of preoperative Ct and other biochemical or imaging tests in MEN 2B children <1 year old is unclear as published data have largely described older MEN 2B children with elevated Ct levels prior to thyroidectomy (58–60,64,176). While some have advocated for prophylactic central neck dissection (with or without lateral neck dissections) in the youngest MEN 2B children (12,58,59,64), its unproven benefits must be balanced against the risk and serious management challenge of hypoparathyroidism in this age group.

- **RECOMMENDATION 32** MEN 2B patients undergoing prophylactic thyroidectomy within the first 1 year of life should have this procedure performed in an experienced tertiary care setting, and preservation of parathyroid function should be given a high priority. Grade: C Recommendation
- **RECOMMENDATION 33** Prophylactic level VI central compartment neck dissection may not be necessary in MEN 2B patients who undergo prophylactic thyroidectomy within the first year of life unless there is clinical or radiological evidence of lymph node metastases or thyroid nodules >5mm in size (at any age), or a serum basal serum Ct>40 pg mL in a child >6 months old; all of which suggests the possibility of more extensive disease that requires further evaluation and treatment (see Fig. 1). Grade: E Recommendation

[B15] Surgery for the youngest MEN 2A or FMTC patients (Fig. 1). The youngest MEN 2A and FMTC patients are 3–5 years of age. In the setting of a normal thyroid examination, it is not clear that these children are benefited by preoperative measurement of Ct, calcium, or neck US because the rates of metastases or PHPT are so low. Still, many clinicians prefer to obtain a preoperative basal serum Ct. If the basal Ct level is less than 40 pg mL it is unlikely that lymph node metastases are present (80,94,177). Frank-Raue *et al.* (80) reported that only one of their five patients who had persistent or recurrent disease after undergoing prophylactic thyroidectomy had a preoperative Ct <40 pg/mL. Scheuba *et al.* (178) evaluated 97 patients with MTC≤1 cm and reported one patient (1%) with lymph node metastases and a basal serum Ct <40 pg/mL. Thus, when the preoperative serum Ct is <40 pg/mL then a total thyroidectomy without central (level VI) neck dissection may be adequate therapy. In this procedure, all thyroid tissue should be removed. This includes the tubercle of Zuckerkandl, pyramidal lobe, and all superior pole tissue. If a thyroid US demonstrates a nodule >5mmin size, or the basal Ct level is over 40 pg/mL (which is unlikely in this age group), there is a higher risk of lymph node metastases (94), and further evaluation prior to intervention is warranted (see Fig. 1). All efforts must be made during surgery to prevent hypoparathyroidism.

- **RECOMMENDATION 34** MEN 2A or FMTC patients who undergo prophylactic thyroidectomy within the first 3–5 years should have this procedure performed in an experienced tertiary care setting, and preservation of parathyroid and recurrent laryngeal nerve function should be given a high priority. Grade: C Recommendation
- **RECOMMENDATION 35** MEN 2A or FMTC patients undergoing prophylactic thyroidectomy within their first 3–5 years should not undergo prophylactic level VI compartmental dissection unless there is clinical or radiological evidence of lymph node metastases, or thyroid nodules >5mm in size at any age, or a basal serum Ct >40 pg/mL (see Fig. 1). Grade: E Recommendation
- **RECOMMENDATION 36** In MEN 2A or FMTC, the clinical or radiological evidence of lymph node metastases or thyroid nodules ≥5mm in size at any age, or a serum basal serum Ct of >40 pg/mL when >6 months old, suggests the possibility of more extensive disease that requires further evaluation and treatment (see Fig. 1). Grade: B Recommendation

[B16] Preoperative imaging and biochemical testing to evaluate for MTC in older RET mutation–positive patients (Fig. 1). Older asymptomatic MEN 2A and FMTC patients are those >5 years of age, while for MEN 2B this cut-off is lowered to >1 year of age. Over these cut-offs, there is an increased possibility that MTC may have already developed and possibly metastasized. In these patients, evaluation should include physical examination, serum Ct, and neck US. The neck US should evaluate the thyroid, as well as the lymph nodes of the superior mediastinum, the central neck, and the lateral neck compartments. Experienced ultrasonographers have a high sensitivity to identifying cervical metastases in adults, especially in the lateral neck, whereas experience with childhood MTC is more limited. Machens *et al.* (94) reported from their series that nodal metastases began to be seen with serum Ct levels of 40 pg/mL, and primary tumors diameters as small as 5 mm. In MTC, the initial site of metastases is typically to cervical lymph nodes. Cervical lymph node metastases, as well as extra-thyroidal extension, are predictors of distant metastases. The basal serum Ct can also indicate the risk of distant metastases (94).

- **RECOMMENDATION 37** In asymptomatic MEN 2A and FMTC patients who present at age >5 years and asymptomatic MEN 2B patients who present at age >1 year, preoperative basal serum Ct and neck ultrasonography should be performed. Grade: B Recommendation
- **RECOMMENDATION 38** In asymptomatic MEN 2A and FMTC patients who present at age >5 years and asymptomatic MEN 2B patients who present at age >1 year, further evaluation prior to surgery and more extensive surgery are needed if the basal serum Ct is >40 pg/mL, if thyroid nodules are ≥5 mm, or if suspicious lymph nodes are identified on neck US. Grade: B Recommendation

[B17] Surgery for the older MEN 2B patients without evidence of cervical lymph node metastases and normal or minimally elevated Ct levels (Fig. 1). Identification of an MEN 2B patient >1 year old with all thyroid nodules <5mm, normal-appearing cervical lymph nodes on US, and a serum Ct level <40 pg/mL would be unusual. Most MEN 2B patients are diagnosed later in life with markedly elevated Ct levels and obvious lymph node metastases (58,59,64,176,179). Two recent series report that the mean age of diagnosis among their MEN 2B patients as 13–14 years old (70,180). In one of these series, 2 of 5 (40%) children operated at age <5 years versus only 1 of 20 (5%) children who were ≥5 years old at surgery were biochemically cured of MTC (70). In a third series of 18 MEN 2B patients (64), the oldest child with disease status of T1N0M0 or less was 3.4 years old. These reports are consistent with other series showing that among MEN 2B children who undergo surgery by age 10 years old about half have cervical lymph node metastases (59,60,64) while still others will demonstrate recurrent or persistent disease during follow-up such that only about one-quarter remain free of disease.

- **RECOMMENDATION 39** In an MEN 2B patient >1 year old with all thyroid nodules <5mmon US and with a serum Ct level <40 pg/mL, a total thyroidectomy is recommended. Grade: A Recommendation
- **RECOMMENDATION 40** In an MEN 2B patient >1 year old with all thyroid nodules <5mm on US and with a serum Ct level <40 pg/mL, inadequate data are available to guide decisions on prophylactic lymph node dissections. Based on expert opinion, the Task Force favored a prophylactic central neck dissection (recognizing that this would likely require auto-transplantation of at least the inferior parathyroid glands), without lateral compartment neck dissection except in the setting of radiographic or clinically proven metastases to these regions. Grade: C Recommendation

[B18] Surgery for the older MEN 2A or FMTC patients without evidence of cervical node metastases and normal or minimally elevated Ct levels (Fig. 1). In an MEN 2A or FMTC patient >5 years old with all thyroid nodules <5mm on neck US and with a serum Ct level <40 pg/mL a prophylactic thyroidectomy is indicated. However, there is no evidence to compel prophylactic lymph node dissections because nodal metastases are unlikely when the basal serum Ct level is <40 pg/mL (80,94,178). Lymph node metastases are uncommon under the age of 11 years (3%), and when they are present their resection may result in long-term biochemical remission in only about one third of these patients, while 6% of all children undergoing central neck dissection may suffer hypoparathyroidism (81). During the thyroidectomy, all thyroid tissue should be removed including the tubercle of Zuckerkandl, the pyramidal lobe, and all superior pole tissue. If the

basal Ct level is >40 pg/mL, there is a higher risk of lymph node metastases, and further evaluation is indicated (see Fig. 1).

- **RECOMMENDATION 41** In an MEN 2A or FMTC patient >5 years old with all thyroid nodules <5mm on neck US and with a serum Ct level <40 pg/mL, a total thyroidectomy is recommended. The age when this is performed is based on the ATA risk level (Tables 5 and 6). Grade: B Recommendation
- **RECOMMENDATION 42** In an MEN 2A or FMTC patient >5 years old with all thyroid nodules <5mm on neck US and with a serum Ct level <40 pg/mL, a prophylactic lymph node dissection is not recommended. Grade: E Recommendation

[B19] Diagnostic testing for RET mutation–positive patients suspected of having metastases based on imaging or serum Ct level.

- **RECOMMENDATION 43** Patients harboring *RET* oncogene mutations who have clinical or radiographic findings suspicious for metastatic MTC, including those with thyroid nodules ≥ 5mm or a serum Ct level >40 pg/mL, should be considered for further evaluation prior to surgery as outlined in Fig. 2. Grade: B Recommendation

[B20] Management for normal parathyroid glands resected or devascularized during surgery. Normal parathyroid glands can be accidentally removed or devascularized during thyroidectomy or central neck lymph node dissection procedures. In all instances, the operating surgeon should be experienced at localizing the parathyroid glands, especially in children, and have expertise with parathyroid autotransplantation. Normal parathyroid tissue should be left in the patient whenever possible, either on an adequate vascular pedicle *in situ*, or if that is not possible, transplanted into the neck or forearm (181). The location to place the transplanted tissue is determined by the type of *RET* mutation present. Patients with a strong family history of PHPT, or with a *RET* mutation associated with a significant risk of PHPT (Table 5), should have the parathyroid tissue placed in the forearm. If the patient has MEN 2B, FMTC or a mutation with a low risk of PHPT (Table 5), the grafts may be placed in the sternocleidomastoid muscle.

- **RECOMMENDATION 44** Devascularized normal parathyroid glands from patients with MEN 2B or FMTC should be autografted into the sternocleidomastoid muscle of the neck. Grade: C Recommendation
- **RECOMMENDATION 45** Devascularized normal parathyroid glands from patients with MEN 2A in a kindred with strong family history of PHPT, or a *RET* mutation carrying a significant risk of PHPT, should be autografted into the forearm. Grade: C Recommendation
- **RECOMMENDATION 46** Devascularized normal parathyroid glands from patients with a *RET* mutation associated with both MEN 2A with a low risk of PHPT and FMTC, whose kindred suggests FMTC, may undergo autograft of the parathyroid tissue into either the forearm or the sternocleidomastoid muscle. Grade: C Recommendation

[B21] Treatment for PHPT in MEN 2A. For the patient who has not had prior neck surgery and has PHPT diagnosed at the time of planned thyroidectomy, surgical options include resection of just the visibly enlarged glands (with a forearm autograft), subtotal parathyroidectomy leaving one or a piece of one gland *in situ* (with a forearm autograft), and total parathyroidectomy with forearm autograft (81,182–184). It is argued that forearm parathyroid autografting should always be performed when parathyroid tissue is removed unless a functioning forearm autograft is known to already be present. This is because of the increased risk that subsequent neck operations will be needed (typically for recurrent MTC) and the remaining *in situ* parathyroid tissue may not be identified and preserved; resulting in permanent hypoparathyroidism. Importantly, most MEN 2A patients with PHPT have undergone prior thyroidectomy (prophylactically or therapeutically for MTC) with or without a complete level VI dissection. Such patients who then develop PHPT should not undergo a neck exploration without preoperative localization (e.g., US, sestamibi, computed tomography [CT]), and in general, only localized, hypertrophied parathyroid glands should be excised. Forearm parathyroid autografting should be performed unless a functioning forearm autograft is known to already be present,

even if intra-operative PTH values suggest the presence of additional parathyroid tissue in the neck. This is because of the risk for MTC recurrence and the need for subsequent neck operations at which time all remaining parathyroid tissue in the neck may be removed with the tumor specimen and not recognized as parathyroid tissue. The result would be permanent hypoparathyroidism; an avoidable complication in most MEN 2A patients if autografting is performed at the first opportunity.

Considering medical therapy, calcimimetics increase the sensitivity of parathyroid calcium-sensing receptors to extracellular calcium, thereby reducing PTHsecretion.Amulticenter, randomized, double-blind, placebo-controlled study has assessed the ability of the oral calcimimetic cinacalcet HCl to achieve long-term reductions in serum calcium and PTH concentrations in patients with PHPT. Cinacalcet rapidly normalized serum calcium and reduced PTH in these patients and these effects were maintained with long-term treatment (185). Cinacalcet may be an effective, nonsurgical approach for management of PHPT, but whether or not these data are applicable to MEN 2A–associated PHPT is uncertain, and data regarding outcomes such as fractures, kidney stones, and cardiovascular disease are not available. However, medical therapy is likely to have an increased role in patients with persistent or recurrent PHPT, and in those who are suboptimal surgical candidates.

- **RECOMMENDATION 47** Because of the high rate of biochemical cure of PHPT in MEN 2A with surgery, initial surgical therapy is preferred to medical therapy, in the absence of contraindications such as excessive surgical risk or limited life expectancy. Grade: C Recommendation
- **RECOMMENDATION 48** Surgical management of PHPT at the time of initial thyroidectomy should always be performed if the diagnosis of PHPT is established. Surgical options include resection of just the visibly enlarged glands (with a forearm autograft), subtotal parathyroidectomy leaving one or a piece of one gland *in situ* (with a forearm autograft), and total parathyroidectomy with forearm autografting. Because of the risk for permanent hypoparathyroidism following one or more neck operations in patients with MEN 2A, combined with the frequent delay in autograft function, forearm parathyroid autografting should always be performed with the initial PHPT surgery. Most experts avoid total parathyroidectomy unless all four glands are obviously abnormal and preservation of an *in situ* parathyroid remnant is not possible. Grade: C Recommendation
- **RECOMMENDATION 49** For patients who are found to develop PHPT after a prior thyroidectomy, operative management should be directed parathyroid surgery and based on the findings from preoperative parathyroid localization studies. Forearm parathyroid autografting should always be performed unless a functioning forearm autograft is known to already be present; even if intra-operative PTH values suggest the presence of additional parathyroid tissue in the neck. Grade: C Recommendation
- **RECOMMENDATION 50** Medical therapy to control PHPT in MEN 2A should be considered in patients with high risk of surgical mortality, limited life expectancies, or persistent or recurrent PHPT after one or more surgical attempts for cure. Grade: C Recommendation

*Stimulated Ct testing historically was done by measuring serum Ct levels at intervals after intravenous administration of the secretagogue pentagastrin and/or calcium (92). Pentagastrin is not available in the United States and many other countries. Additionally, newer calcitonin assays have significantly improved functional sensitivities, currently as low as 1–2 pg/mL. Resultingly, most experts believe that there is rarely a need for stimulated Ct testing in the diagnosis or follow-up of MTC.

*See footnote, page 574.