Narrative Review Article

RET Gene Mutations in Infants: A Literature Review of Implications on MEN2 syndrome

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ABSTRACT

MEN2 is a rare autosomal dominant endocrine cancer syndrome caused by germline mutations in the RET proto-oncogene and includes three subtypes — MEN2A, MEN2B and fMTC — which all carry the risk of medullary thyroid carcinoma (MTC) in infants. This narrative review synthesizes current research on RET mutations, malignancy risk, long-term outcomes, current treatments and newborn screening ethics. Findings indicate that the malignancy risk is largely related to the RET mutation subtype, with MEN2A being the most common accounting for 55% of cases and MEN2B presenting the most aggressive progression in infancy. An early diagnosis done through the use of CT and CEA biomarkers leads to an early form of treatment, usually an early prophylactic thyroidectomy and substantially decreases the risk of metastasis and mortality, though lifelong surveillance is required for some possible long-term outcomes. In addition, the diagnosis of MEN2A in infants often requires screening which raises many important ethical, clinical and social dilemmas especially in parental decision-making and equitable care. The review highlights the importance of genetic testing for at-risk infants and timely surgery to reduce mortality. Disparities in healthcare access and strengthening long-term outcomes to improve care for children with MEN2 could be addressed in future research.

Keywords: Medullary thyroid carcinoma (MTC); Multiple endocrine neoplasia type 2 (MEN2); Rearranged during Transfection proto-oncogene (RET); Pediatric

INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN2) (1) is a rare, inherited autosomal dominant endocrine cancer syndrome caused by germline mutations in the REarranged during Transfection (RET) proto-oncogene (2). The RET gene encodes for transmembrane receptors of the tyrosine kinase family and mutations can lead to continuous activation of this receptor and promote uncontrolled cell growth, especially in the thyroid's parafollicular C cells (3). MEN2 is classified into three different subtypes: MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC) (2). Every subtype carries a lifetime risk of medullary thyroid carcinoma (MTC), a malignant tumor of the thyroid's parafollicular C cells. MEN2B is particularly associated with a more aggressive form of development and is often expressed during infancy and progresses rapidly without a timely diagnosis or an intervention (3).

Although MTC only represents a small fraction of pediatric thyroid cancers, it is the primary cause of morbidity and mortality in MEN2 (4). In infants and children, the malignancy risk and tumor development

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are strongly influenced by the type of RET-mutation and therefore the MEN2 subtype. Even though RET genetic testing and newborn screening are accurate in identifying possible mutations in at-risk children, ethical considerations, particularly regarding parental consent and autonomy, can influence parental decision on testing (5). The overall recommendations remain early prophylactic thyroidectomy once the mutation has been identified as the most effective treatment against the disease because chemotherapy is not yet effective for this type of cancer (3).

This literature review presents the current findings on RET mutations in pediatric MEN2 syndrome, with a focus on malignancy risk in infants and the long-term outcomes of this disease as well as the ethical concerns for newborn screenings.

GENETIC RISK OF MEN2 SYNDROME AND RISK OF MALIGNANCY

MEN2 is a rare hereditary endocrine cancer syndrome with an incidence estimated at around 1 in 200 000 live births and caused by mutations in the RET proto-oncogene. MEN2 includes three subtypes: MEN2A, MEN2B and FMTC which are all inherited in an autosomal dominant manner with variable penetrance in the RET proto-oncogene (4). Symptoms, including gastrointestinal symptoms and musculoskeletal clinical features will be discussed in the next section.

Each subtype of MEN's disease is associated with a germline RET mutation and around 50% of sporadic MTC show somatic RET mutations. In addition, 50% of children born to a parent with an RET mutation have a risk of inheriting it and developing MEN2 syndrome. Because patients with MEN2 have a 100% lifetime risk of developing MTC before the age of 70, MTC has become the most important factor of mortality in these patients.

Every MEN2 subtype is associated with a unique RET gene mutation that acts by consistently activating the kinase. In research done in North America, around 85% of patients carrying MEN2 have a mutation at the exon 11 codon 634 of the RET gene while 10-15% of other cases are linked to mutations in codons 609, 611, 618, and 620 . MEN2A is the most common subtype of MEN2 as it accounts for around 55% of cases (4). Patients with MEN2A may also carry RET gene mutations in exons 7 and 8. A 2014 study of 250 MEN2A patients done in Denmark concluded that C611Y was the most common mutation (68%), followed by C618Y (6%) and C611W (6%), among others (7). The majority of the cases had inherited their RET mutation as only one case (the C620R mutation) was characterized as *de novo*. In this study, they reported an incidence of MEN2A of 28 per million live births a year, making this subtype an already extremely rare disease. Additionally, 20-30% of patients with MEN2A can develop primary hyperparathyroidism which can be treated through surgery (4).

MEN2B is both the most aggressive and rarest subtype of MEN2 as it accounts for around 5-10% of all cases. While germline RET mutations are present in all MEN2B patients, generally coming from the father, about 50% of MEN2B cases are generated from *de novo* mutations without a previous family history, meaning the mutation happens spontaneously rather than being inherited (4). Most patients carrying MEN2B have RET gene mutations in codon 918 exon 16 and rarely in codons 883 (A883F mutation), 644 (T644M mutation) and 922 (8). While the M918T mutation has been associated with particularly aggressive MTC behavior and metastases, the A883F mutation has been characterized as less aggressive and associated with milder symptoms. The epidemiology of MEN2B is relatively unknown but its prevalence is estimated at around 1 in 600,000 to 1 in 4 million cases while the annual incidence has been estimated at around 4 per 100 million per year (8).

Overall, more than 50 distinct RET gene mutations across 7 exons (8, 10, 11, 13–16) have been identified with different mutations carrying various risks based on the age of onset, aggressiveness and progression of the disease, and presence of associated endocrine neoplasms (4). The C634 and M918T mutations, associated with MEN2A and MEN2B respectively, are strongly linked to early metastasis and an aggressive development of the disease. In addition, depending on the RET mutation, 50% of patients develop pheochromocytomas, and 30% develop primary hyperparathyroidism (4).

DIAGNOSIS AND PRE-OPERATIVE STAGING

Early diagnosis in MEN2 syndrome is vital for improving the long-term outcomes as the only curative treatment is surgery, more specifically prophylactic thyroidectomy performed before metastatic progression (2). Because of the nonspecific symptoms associated with MEN2 in infants and the rarity of the disease, the diagnosis is frequently delayed. Different features such as clinical features, the use of biomarkers, and

genetic testing allow for early recognition and prevent complications of the disease in children with MEN2 (Table 1).

Regarding the clinical features present often from birth or early infancy, gastrointestinal symptoms including chronic constipation, severe pseudo-obstruction or pseudo-Hirschsprung disease, secretory diarrhea and abdominal distention are present in more than 80% of early MEN syndrome (9). Recognizable oral and facial symptoms in infancy include full or thickened lips, gingival hyperplasia, a high arched palate, and mucosal ganglioneuromatosis, which is essentially buccal mucosa on the tongue and lips. Alacrima, or the absence of tears, has also been seen in 80-85% of affected children.

Musculoskeletal features including joint hypermobility, hypotonia, marfanoid habitus and delayed motor milestones reinforce clinical suspicion of MEN2 syndrome (9). A histological analysis, meaning the "study of tissues and cells under a microscope" can also support an early diagnosis (6). The presence of Intestinal Ganglioneuromatosis (IG) on rectal or GI biopsies, characterized by a large submucosal ganglion and calretinin and synaptophysin positive nerve fibers, should prompt urgent RET sequencing and/or genetic testing for RET mutations (9).

Calcitonin (CT) is the primary biochemical marker used in diagnosing MTC. It reflects C-cell burden and remains useful in diagnosing the disease, surgical timing, and postoperative monitoring (3). Elevated CT levels (>800 ng/L in some advanced cases) are strongly suggestive of MTC (9). The doubling time of calcitonin serves as a prognostic indicator showing the rate at which CT levels increase and using those to predict how aggressive the cancer is. Carcinoembryonic Antigen (CEA), though less specific, provides additional value in the diagnosis when both markers are elevated. CEA is often elevated in more advanced diseases (e.g., 258 μg/L) and is therefore often more useful in those cases. Plasma metanephrines can also be evaluated as they are used to screen tumors related to MEN2, in particular pheochromocytoma (PHEO), an adrenal gland tumor that produces large amounts of catecholamines (3).

RET genetic testing is also crucial and conclusive for MEN2 diagnosis. For instance, The p.Met918Thr mutation in exon 16 is found in nearly all MEN2B cases and arises de novo in 84–100% of patients (9). Additionally, preoperative imaging plays an important role in staging diagnosis. Thyroid imaging may reveal multiple calcified thyroid nodules, extrathyroidal extension, and / or enlarged cervical lymph nodes which all point towards a possible MEN2 diagnosis. Once thyroid nodules are identified, Fine Needle Aspiration (FNA) can confirm the diagnosis in ⅔ cases pre-op. At the time of the diagnosis, many children already have advanced-stage MEN2 (Stage III–IVC) with lymph node involvement and possible distant metastases in the lungs, liver and mediastinum (9). To conclude, an early diagnosis is critical in the survival of MEN2, with the recognition of early clinical signs as an important step towards recovery.

ETHICAL CONCERNS OF SCREENING IN NEONATES

Genetic screening for RET gene mutations in infants has raised many important ethical, clinical, and social dilemmas. Compared to biochemical testing, RET genetic testing is more sensitive and has been shown to greatly reduce the rate of MTC in children and other individuals with MEN2 hereditary syndrome (10). Oftentimes, clinical associations and doctors recommend genetic testing as it is currently the only effective step towards prevention and early treatment of the disease, with prophylactic therapy being a standard of care for individuals who tested positive (10). MTC

Table 1. Summary of MEN2 Syndrome Manifestations and Management

Manifestation of MEN2 Syndrome	Treatment/Management
MTC	Calcitonin level monitoring → prophylactic thyroidectomy and lifelong surveillance (calcitonin, CEA, neck ultrasound)
Pheochromocytomas	Biochemical screenings (metanephrine level monitoring) → excisions
Hyperparathyroidism	Calcium and parathyroid hormone level monitoring → screening
Metastatic MTC	Use of MKI's (vandetanib, cabozantinib) and RET inhibitors (Selpercatinib, Pralsetinib)
Skeletal / Gastrointestinal features	PPRT targeting somatostatin and cholecystokinin-2 receptors

meets all 10 Wilson-Jungner criteria (11) for public health screening, a classic criterion for screening, so RET gene testing after birth and later is recommended in high-risk children. The "reasonable person standard" suggests that informed people should choose testing, but the uptake still remains below 100% because a significant number of at-risk children are unaware or untested possibly due to the lack of notification and information the guardian holds (10). One newborn who tests positive for RET mutation can identify other at-risk individuals with the estimated impact showing that 1000 screened newborns could lead to the prevention of 5,000 cases of MTC annually (10).

Many social, ethical, and systemic barriers exist and also prevent individuals from turning towards genetic screening. This can include literacy, education, income, cultural and religious beliefs, family dynamics, and limited healthcare access and incomplete genetic counseling (10). The Health Insurance Portability and Accountability Act (HIPAA) (12) protects the patient and their guardian's privacy even if other family members are at-risk, meaning relatives may stay uninformed and untested. Some physicians may breach this privacy and contact family members, which is an approach that is both ethically and legally unresolved. Inadequate genetic counseling has also led to the misunderstanding of test implications which lowers the uptake and variants of unknown significance also complicate the RET gene testing interpretation and further decisions regarding the patient. In addition, late-stage diagnoses are expensive (standing at around $7,282/month per patient) which can raise questions about its accessibility (10).

Informed guardian or parent consent is required for pediatric screening. Because of lack of information, barriers, and other reasons previously mentioned, many parents can and do refuse procedures for their children, particularly genetic testing (5). Newborn screening programs don't necessarily require explicit consent which can also raise concerns about autonomy and informed decision-making. Broader concerns can include the secondary findings that are uncovered during genetic screenings (5). The American College of Medical Genetics recommends reporting such findings, even without consent, which raises ethical concerns especially as another association, the American Society of Human Genetics (13) , advocates for targeted testing and consent-based disclosures of adult-onset risks. In addition, risks of psychosocial harm (anxiety, identity crises) are also raised for children taking these tests (5). Ultimately, a child's future autonomy must be respected and balanced with informed parental decision-making and equitable care.

LONG-TERM OUTCOMES OF MEN2

Long-term outcomes for children affected by MEN2 syndrome, those with RET mutations in particular, are closely tied to the timing and effectiveness of the surgery. In infants affected by MEN2, early prophylactic thyroidectomy significantly improves the recovery, life expectancy, and reduces potential long-term outcomes (2). In many positive cases, patients can resume work, hobbies, exercise, and other normal activities after recovery (18). If the surgeon removes all the parathyroid glands during an operation, the patient will need to take thyroid hormone replacement medication for the rest of their lives to control calcium levels and metabolism (17, 18). A German cohort study (n=167) reported a 99% biomedical cure rate (postoperative normalization of elevated calcitonin levels) on the MTC tumor when the surgery was performed early and prophylactically (3). In children with MEN2B, early surgery once again reported better biochemical cure rates and effect on the tumor: biochemical remission in 83% of cases before the age on one compared to biochemical remission in 15% of cases where the surgery was done after the age of one (3). Nevertheless, surgical complications do exist with transient hypoparathyroidism occurring in 18–49% of cases, depending on the series. After surgery and potential recovery, post-operative surveillance and lifelong follow-ups are necessary to ensure the patient does not relapse. This can include regular physical examinations and biochemical monitoring of serum calcitonin (CT) and CEA every 6 to 12 months. Additional imaging can be conducted if the VT levels exceed 150 pg/mL (3). In addition to physical health, mental health (sadness, anxiety, frustration, depression) is also managed post-operation as the recovery can be difficult for both the patient and the family (18).

As MEN2 often correlates with other diseases, screenings for pheochromocytoma (adrenal gland tumor) and other labs such as the measurement of plasma or urinary metanephrines can start at the age of 11 of extremely high-risk patients or at the age of 16 for patients having a moderate risk (3). Hyperparathyroidism, an increase in parathyroid hormone levels in the blood (14), has also affected around 30% of children with MEN2A and is monitored through calcium and parathyroid hormone levels (3).

Screenings for this complication can begin at age 11 or 16, once again depending on the risk category.

Overall and most importantly, children with MEN2 tend to have higher complication rates with these surgeries than adults because organs in a child's body may still be developing and might differ from that of adults (15). Additionally, despite an early intervention and surgery, metastasis of MTC cannot be prevented in all cases, especially in MEN2B. According to a 2024 study (16), the median follow up to last known vital status in pediatric patients was 12.8 years, with a median overall survival of approximately 34.2 years for children with MTC, around 39.3 years for children with MEN2B. Patients with MEN2A had better long term outcomes, with no significant impacts on mortality during the study duration, especially with appropriate early surgical interventions.

ESTABLISHED AND NOVEL TREATMENTS FOR INFANTS

The cornerstone of treatment for infants diagnosed with MEN2 syndrome, MEN2A and MEN2B in particular, remains early prophylactic surgery, a surgical procedure that is performed "to reduce the risk of developing a disease, often cancer, before it has a chance to occur" (6). The standard treatment remains a total thyroidectomy to prevent MTC before it becomes invasive (3). Depending on the central lymph node involvement, central neck dissection can be considered, but is often avoided in children to reduce risk of injury to parathyroids, recurrent laryngeal nerves, and risk of hemorrhage (2). Early surgeries can be critical in high-risk cases such as for MEN 2B and the RET mutation of codon M918 where a total thyroidectomy is necessary within the first 6 months or year of life because of the aggressive nature of the disease (3).

In MEN2A cases with C634 mutations, a surgery is typically performed within the first 5 years of life if basal serum calcitonin (serum CT) levels exceed 40 pg/ml or if there is evidence of affected lymph nodes (2). In other cases of RET mutations and MEN's disease, the ATA (9) suggests using CT levels to monitor the spread of the disease and indicate the treatments to use. If the CT levels are found to be high, a lateral neck dissection must be considered and if the CT level exceeds 200 pg/mL and there is ipsilateral node positivity, a contralateral dissection may be necessary (2).

Despite the intervention of surgery, the disease may be recurrent (CT levels rise after normalization indicating tumor aggressiveness) or even persistent (CT levels remain elevated post-op and indicate inadequate resection) and necessitates further intervention through surgery or targeted therapies (2). These can firstly include the use of multikinase inhibitors (MKIs) such as vandetanib and cabozantinib to decrease tumor growth and replication. The MKIs are used for progressive metastatic MTC and usually hold modest efficacy and are not necessarily RET-specific. Other targeted therapies include highly selective RET inhibitors such as Selpercatinib (LOXO-292) and Pralsetinib (BLU-667). In contrast with the MKIs previously mentioned, these inhibitors are RET-specific and have demonstrated response rates of up to 70% even in patients with prior MKI failure (2). They are approved for progressive and advanced MTC and are being explored in neoadjuvant settings to shrink the tumor before resecting it in surgery and resume the previous therapy. In a July 2025 case report of a 65-year-old man with micro-MTC initially presenting as cancer of unknown primary (CUP), the identification of a M918T RET mutation prompted a switch to 320 mg of selpercatinib daily. This led to a rapid and significant reduction in cervical lymphadenopathy and serum calcitonin within one week which demonstrated the therapeutic efficacy and responsiveness of RET-inhibitor therapy in RET-mutated MTC (20). In MEN's cases, external radiotherapy and traditional chemotherapy have primarily had low responses and are considered less effective than MKIs or RET inhibitors. Additionally, emerging therapies are under investigation in their impact on MEN's disease in different child patients. These include Peptide Receptor Radionuclide Therapy (PRRT) which targets somatostatin and cholecystokinin-2 receptors and has had stable or partial response in up to 60% of cases, radioimmunotherapy using anti-CEA monoclonal antibodies, and immunotherapy using pembrolizumab, nivolumab, or ipilimumab and other experimental substitutes as checkpoint inhibitors (2). Notably, a recent 2025 study of 177 Lu-DOTATATE PRRT in patients with gastroenteropancreatic neuroendocrine tumors showed 43% objective response rate (ORR) and a median progression-free survival (PFS) of about 32.6 months, demonstrating that PRRT is a promising technique for managing advanced neuroendocrine tumors in MEN2 syndrome and other similar diseases (19). CAR-T therapy has also been tested in targeting GFRα4 which is overexpressed in MTC and mouse models have shown tumor elimination. Finally, CRISPR gene editing seems promising for understanding

RET-driven tumor biology and therapeutic targets. Moreover, recent medical advances, including the GLP1 medications which have shown promising results in the setting of cardiovascular health and glycemic control, provides a complicated landscape for patients with MEN2B as they are strongly discouraged in individuals with a personal or family history of MTC or MEN2 and are potentially associated with an increased incidence of differentiated thyroid cancer (DTC) in these patients. However, findings do remain conflicting (21).

CONCLUSION

This literature review highlights that mutations in the RET proto-oncogene are the primary driver of MEN2 syndromes, including MEN2A and MEN2B, and are strongly related to the development of MTC (2). In infants, the risk of malignancy largely depends on the predispositions, meaning the inherited germline mutations, and the RET-mutation subtype, with MEN2B cases demonstrating a particularly aggressive clinical form of development. However, findings surrounding the most common RET germline mutation leading to MEN2A conflict as one 2015 study done in North America concluded that around 85% of patients carrying MEN2 have a mutation at the exon 11 codon 634 of the RET gene (4) and another 2018 study done in Denmark concluded that C611Y was the most common RET mutation (68%) leading to MEN2A (7). The study of the sources and research shows that early prophylactic surgery, more specifically a thyroidectomy, significantly reduces the risk of metastasis and improves long-term survival in affected infants (2, 3). However, even when a surgery has been done, the necessity for lifelong surveillance remains, along with the long-term outcomes that follow this disease (2).

The numerous articles cited in this review reinforce the understanding that only an early diagnosis and genetic identification can rapidly lead to surgery and reduce the mortality of MEN2 in high-risk infants (2, 12). The assembled findings also point to numerous risks and complications that arise with a diagnostic delay. A challenge remains in equalizing and advocating for surgical timing across healthcare systems, especially in regions with financial limitations and therefore limited access to genetic testing and pediatric surgery. Additionally, the lack of long-term MEN2 pediatric outcome data leaves gaps in understanding the life-long impact of this disease and the treatments associated with it, particularly a thyroidectomy and its effect on growth, neurodevelopment and psychological well-being (5). In addition, surgical timing suggestions found in studies differ as the common suggestion remains performing a thyroidectomy within the first year of life, especially with the RET mutation of codon M918 which leads to an aggressive form of MEN2B (3) while ATA guidelines (9) suggest using CT levels to monitor the spread of the disease and indicate the treatments to use (2). Policy makers and healthcare corporations should prioritize funding for universal access to genetic counseling and testing, especially for high-risk newborns and their families, and support research into less invasive treatments such as targeted molecular therapies and improved surgical safety in pediatrics. Future research can include refining surgical safety in infants but also accelerating the development of targeted RET inhibitors to completely reduce the tumor and avoid relying on early onset aggressive surgery.

This narrative review is subject to several limitations. Firstly, the availability of studies, research and literature on MEN2 in pediatric populations remains somewhat scarce because it is a rare disease and most resources focus on adult cases of this disease. As a result, some recent or ongoing studies may not have been included in this review and certain information might have been overlooked. In addition, as many studies focused on adult cases due to the fact that it may be difficult to recruit large numbers of pediatric patients, direct comparison between adult and pediatric outcomes may be misleading as the disease often develops earlier and more aggressively in children and requires different treatment timing and prognostic implications compared to adults. Next, as the studies are often limited in number and based on previous findings, leading to few randomized control trials and making it difficult to establish how effective treatments are from one another. Finally, most of the studies follow patients for 10-15 years which leads to gaps in long-term outcome data especially centered around growth, neurodevelopment, and psychosocial well-being after early thyroidectomy, further limiting conclusions.

The evidence presented calls for all parents and other at-risk family members to take genetic tests and spread awareness of the development of this disease when their child is affected. In addition, it is ethically imperative that screenings and other genetic tests be presented to parents and guardians for an early identification of RET mutation-positive infants, all the while acknowledging that parental autonomy and informed consent must remain central in making such a decision. Early

detection, besides preventing advanced diseases, allows parents and patients to make proactive and informed healthcare decisions that can affect an entire family.

It remains important to note that ethical considerations, particularly informed consent, are a central aspect of healthcare because they respect the patient's autonomy and decisions regarding their disease, beliefs and preferences. Because infants and young children cannot provide informed consent, parents or legal guardians act as surrogate decision-makers, meaning they are responsible for making healthcare decisions on behalf of their minor children. Healthcare providers ensure their decisions balance the child's best interests with medical recommendations and cultural, religious, or personal beliefs (22). In certain situations, especially involving older children and adolescents, the mature minor doctrine is involved, meaning minors hold enough maturity to understand the situation and make informed decisions about their own care. In some life-threatening situations, courts can intervene when the parental decisions do not respect the child's best interests (22). Adolescents' individual preferences and beliefs should be acknowledged whenever possible when making decisions about their disease or treatment. Cultural, religious, and personal beliefs can also strongly influence healthcare decisions, especially genetic testing and surgical interventions. It remains extremely important for physicians to respect family beliefs while advocating for the child's well-being to help parents make decisions that consider the child's safety or access to necessary care (22).

Families must be supported in openly communicating genetic risks with relatives because one positive test in an infant can have implications across generations. Healthcare professionals play an extremely important role in providing clear and consistent counseling, presenting surgical risks, and ensuring the continuity of surveillance through adulthood. This highlights the need for enhanced training of pediatric endocrinologists, surgeons, and genetic counselors, so that families can receive specialized, evidence-based guidance at every step of care instead of making decisions with a lack of information. Ultimately, the prevention of MTC in infants with RET mutations relies on a coordinated approach that includes early identification, timely intervention, and long-term patient and family care. In conclusion, the early identification of RET mutations and early prophylactic surgery remain the most decisive factors in reducing mortality from MEN2-associated MTC in infants.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest related to this work

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