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# Should we worry about elevated $B_{12}$ levels in children?

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## Abstract

**Background:** Vitamin $B_{12}$ ($B_{12}$) is an essential nutrient for DNA synthesis and cell metabolism. While $B_{12}$ deficiency has been extensively studied, the importance of elevated $B_{12}$ is under investigation. High levels are described in adults with malignancies and many other conditions. Limited and conflicting data exists pertaining to children with elevated levels.

**Methods:** A single institution retrospective study was conducted. Patients younger than 18 years with high $B_{12}$ levels during the period of 2010-2018 were included. Patients with a history of or concurrent $B_{12}$ therapy were excluded. $B_{12}$ levels, complete blood cell counts, concurrent, prior and future diagnoses were collected.

**Results:** A total of 384 patients with high $B_{12}$ levels were identified. An indication for obtaining a $B_{12}$ level was documented for 296 patients (77.1%) with most common reasons being fatigue (n = 36, 12.2%), failure to thrive (n = 32, 10.8%) and anemia (n = 25, 8.4%). Seven indications, (2.4%) were obtained as follow-up of a previous malignancy. Within the 5 year follow up 47.8% of patients (n=142) had documentation of future diagnoses. The top 3 subspecialties with future diagnoses were psychiatry (n=53, 23.0%), gastroenterology (n=32, 13.9%) and neurology (n=26, 11.3%). Only one patient developed an oncologic diagnosis, Langerhans Cell Histiocytosis.

**Conclusion:** Our study found no association of elevated $B_{12}$ with pediatric malignancies. However, we highlight a possible link between elevated $B_{12}$ and neuropsychiatric and gastroenterological processes. More studies are needed to further delineate the importance of elevated $B_{12}$ in the pediatric population.

## Introduction

Vitamin $B_{12}$, also referred to as cobalamin (Cbl), is an essential vitamin derived from the diet and is tightly regulated in the body. It serves as a cofactor for intracellular synthesis of succinate & methionine, two important intermediates in DNA and RNA synthesis. Its deficiency has been extensively studied and linked to hematological, neurological, and gastrointestinal disorders in adult literature, but there has not been as robust of a focus on states of elevated vitamin $B_{12}$ levels [1,2]. In adults, associations have been made between hypercobalamin and hematological malignancies, solid tumors, liver disease, renal disease, autoimmune disease, and infectious diseases [3]. Specifically regarding hematological and oncological diseases, high serum cobalamin is frequently observed in myeloproliferative disorders, including myelodysplastic syndromes, chronic myelogenous leukemia, primary hyper-eosinophilic syndrome, and acute leukemias, notably promyelocytic leukemia.

In pediatrics, there is no such consensus and there is very limited and conflicting data hypothesizing correlations between vitamin $B_{12}$ levels and cancer. In a small study by Skaff, *et al.* in July of 1966, serum $B_{12}$ levels were measured in twelve pediatric patients with myelogenous leukemia.[4] The levels were elevated in five of eight children with chronic myelogenous leukemia and one of four patients with acute myelogenous leukemia [4]. In 2013, Aleksic, *et al.* published an article with findings of no significant difference between vitamin $B_{12}$ levels of patients with malignant solid tumors versus those with lymphoproliferative or myeloproliferative malignancies. He instead noted a statistically significant increase in $B_{12}$ levels after treatment in both groups [5]. However, more recently in 2015, vitamin $B_{12}$ levels were noted to be significantly lower in children with newly diagnosed solid tumors than their healthy counterparts [6]. As such, no true consensus exists regarding the clinical implications of elevated vitamin $B_{12}$ levels in children. Given the significant associations with hematological and oncological malignancies in adults as well as the conflicting data in the pediatric population, this study was performed to more clearly elicit the indication for obtaining vitamin $B_{12}$ levels in pediatrics, understand the role of vitamin $B_{12}$ levels in pediatric malignancies, and attempt to identify alternate associated comorbidities.

## Methods

An IRB-approved, single institution retrospective study was conducted via electronic chart review from 2010 to 2018. Patients younger than 18 years with abnormal vitamin $B_{12}$ levels defined as less than 211 pg/mL or greater than 911 pg/mL were included in this study. Exclusion criteria for this study were: either a history of vitamin $B_{12}$ therapy or concurrent vitamin $B_{12}$ therapy at the time of abnormal vitamin $B_{12}$ level. Patients with low $B_{12}$ levels were excluded from the analyses. In addition to serum vitamin $B_{12}$ levels, complete blood counts and inflammatory markers, including c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were collected and analyzed

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if obtained at the same time as the abnormal $B_{12}$ level. Additional data gathered through chart review included the indication for obtaining a vitamin $B_{12}$ level, any prior or concurrent diagnoses, and any documented future diagnoses. The indication for obtaining a $B_{12}$ level was found either documented in physician notes or by indication reported on diagnostic lab requisition. Prior diagnoses were defined as all diagnoses documented up to five years prior to abnormal vitamin $B_{12}$ level. Similarly, future diagnoses were defined as any diagnosis documented up to five years following abnormal vitamin $B_{12}$ level. The indications for obtaining a vitamin $B_{12}$ level, prior diagnoses, and future diagnoses were further categorized as constitutional or by subspecialty.

Patient demographics and clinical characteristics are reported using mean with standard deviation or median, interquartile ranges for continuous variables. Categorical variables are reported with frequencies and percentages, as appropriate. We used the Spearman Correlation coefficient to assess the correlation of the $B_{12}$ levels with the continuous variables (age and several hematologic parameters) and Mann Whitney U test for the binary variables. P-values less than 0.05 were considered statistically significant for the analysis. The analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC) and R software, version 4.0.0.

## Results

A total of 497 patients' records were screened based on inclusion criteria for the study. One hundred and eight patients were excluded based on exclusion criteria described above.

A total of 389 patients had abnormal $B_{12}$ levels of which 99% (n = 384) had elevated vitamin $B_{12}$ levels and five patients had low levels. These patients were excluded from subsequent analyses. The baseline characteristics of the cohort are shown in Tables 1 and 2. One hundred ninety-nine patients (51.8%) were female and one hundred eighty-five (48.2%) were male. The median age was 8 years and the interquartile range was [3 years, 13 years].

The results of the correlation analyses predicted hemoglobin (B = -0.119, p = 0.02), White blood cell count (WBC) (B = 0.124, p = 0.02) and CRP (B = 0.364, p = 0.03) to be the significant predictors of vitamin $B_{12}$ levels. The analysis showed a very weak linear relationship where a negative correlation with hemoglobin and the positive correlation with WBC and CRP has been established. Platelet count (B = 0.068, p = 0.213), ESR (B = -0.028, p = 0.82) had no correlation with vitamin $B_{12}$ levels."

**Table 1.** Demographic Characteristics of Patients with Elevated $B_{12}$ Levels (n = 384)

| Characteristic | N (%) | *p* |
|---|---|---|
| Gender Distribution<br>Males<br>Females | <br>199 (51.8%)<br>185 (48.2%) | 0.3007* |
| Age at Encounter, Years<br>Mean<br>Median | <br>8.4 ± 5.5<br>8 (3, 13) | 0.0001† |

*Mann-Whitney u test; †Spearman correlation co-efficient

**Table 2.** Hematological Parameters and Inflammatory Markers

| Variable | N | Value | Correlation | *p*† |
|---|---|---|---|---|
| White Blood Cell Count | 355 | 8.0 ± 3.4 | 0.124 | 0.0236 |
| Hemoglobin | 355 | 12.3 ± 1.9 | -0.119 | 0.0293 |
| Platelet Count | 334 | 313.0 ± 118.7 | 0.068 | 0.2135 |
| CRP | 35 | 5.3 ± 6.8 | 0.364 | 0.0375 |
| ESR | 71 | 12.52 ± 17.99 | -0.028 | 0.8226 |

†Spearman Correlation Co-efficient

An indication for obtaining a $B_{12}$ level was documented for 296 patients (77.1%). Of patients with documented indications, the most common reasons for obtaining a vitamin $B_{12}$ level were fatigue (12.2%), failure to thrive (10.8%), and anemia (8.4%). Fatigue and failure to thrive fell under the category of constitutional indications, which comprised of 31.8% of all indications, followed by indications categorized under gastroenterology (27.4%), and hematology/oncology (12.8%) as shown in Table 3. Combined, these three categories comprised 72.0% of all indications. Seven indications, 2.4%, were reportedly obtained secondarily as follow-up of a previously diagnosed malignancy. Malignancies included Acute Lymphoblastic Leukemia, Diffuse Large B Cell Lymphoma, Ewing Sarcoma, Hypothalamic Pilocytic Astrocytoma, Metastatic Medulloblastoma, Rhabdoid Tumor, and Wilms Tumor.

From the patients with elevated vitamin $B_{12}$, 280 patients (72.9%) had one or more documented prior diagnoses. The most common prior diagnoses were Attention-Deficit Hyperactivity Disorder (ADHD) (7.8%), Developmental Delay (6.4%), and Gastroesophageal Reflux Disease (GERD) (5.7%). Neurological (26.0%), Psychiatric (7.9%) and Gastroenterological (16.0%) diseases comprised of more than the majority of prior diagnoses (59.9%) as shown in Table 4. Only 4.5% of the reported prior diagnoses were hematologic in nature. Other than the seven known cases for which malignancy was the initial indication for measuring vitamin $B_{12}$, no additional prior diagnosis of malignancy was identified.

Within the full five-year follow up for future diagnoses, 47.8% of patients had documentation of an additional diagnosis. The top three subspecialties with future diagnoses were psychiatry (23.0%), followed by gastroenterology (13.9%), and neurology (11.3%) (Table 5). These three categories combined made up approximately half (48.2%) of all future diagnoses identified in patients with elevated $B_{12}$ levels. Aside from these subspecialties, Vitamin D deficiency was the single most diagnosed disease out of all categories (8.3%). This was followed by anemia (7.0%) and ADHD (6.5%). Only one patient developed a future oncologic diagnosis, Langerhans Cell Histiocytosis (LCH). Of the 384 patients with elevated Vitamin $B_{12}$ levels, 24 patients (6.3%) were referred to a hematology/oncology clinic for further work-up.

## Discussion

Primary care physicians are the first line of defense for preventative care and treatment of patients. However, more often than not, they are faced with the complexity of accurately ordering laboratory testing, interpreting the results and effectively using these values to guide clinical management, especially in settings of limited evidence based medicine [7]. Vitamin $B_{12}$ deficiency has been well studied and is known to present with a vast majority of symptoms and signs, including but not limited to: fatigue, failure to thrive, and anemia, which were also the top three most cited indications for obtaining a vitamin $B_{12}$ level in our study [8]. As such, our study suggests that serum $B_{12}$ levels were obtained routinely with the intention to screen for deficiency in the presence of symptoms or other risks. However, it is also important to note that a serum level was obtained for twelve various subspecialty indications, with health maintenance cited as the fifth most common indication. Current pediatric guidelines for infants, children and adolescents as set forth by the American Academy of Pediatrics does not include testing for vitamin $B_{12}$ as part of routine screening for children who have a healthy diet satisfying adequate nutritional needs, have no manifestations of any important health problems, and are growing and developing in a satisfactory fashion [9]. Thus, given the

**Table 3.** Indications for Obtaining $B_{12}$ Levels

| **Constitutional** | **N** | **%** | **Gastroenterology** | **N** | **%** | **Hematology/ Oncology** | **N** | **%** |
|---|---|---|---|---|---|---|---|---|
| **Overall** | **94** | **31.8** | **Overall** | **81** | **27.4** | **Overall** | **38** | **12.8** |
| Fatigue | 36 | 12.2 | Concern for Nutritional Deficiency | 23 | 7.8 | Anemia | 25 | 8.4 |
| Failure to Thrive | 32 | 10.8 | Celiac Disease | 10 | 3.4 | Malignancy | 7 | 2.4 |
| Health Maintenance | 12 | 4.1 | Abdominal Pain | 9 | 3.0 | Thrombocytopenia | 3 | 1.0 |
| Abnormal Weight Loss | 3 | 1.0 | Inflammatory Bowel Disease | 9 | 3.0 | Eosinophilia | 1 | 0.3 |
| Fever | 2 | 0.7 | Diarrhea | 4 | 1.4 | Macrocytosis | 1 | 0.3 |
| Syncope | 2 | 0.7 | Feeding Difficulty | 4 | 1.4 | Pulmonary Embolism | 1 | 0.3 |
| Abnormal Hearing Screen | 1 | 0.3 | Constipation | 3 | 1.0 | | | |
| Brittle Hair | 1 | 0.3 | GERD | 3 | 1.0 | | | |
| Exposure to Smoke | 1 | 0.3 | Irritable Bowel Syndrome | 2 | 0.7 | | | |
| Irritability | 1 | 0.3 | Malabsorption | 2 | 0.7 | | | |

**Table 4.** Prior Diagnoses of Patients with Elevated $B_{12}$ Levels

| **Neurology** | **N** | **%** | **Psychiatry** | **N** | **%** | **Gastroenterology** | **N** | **%** |
|---|---|---|---|---|---|---|---|---|
| **Overall** | **151** | **26.0** | **Overall** | **104** | **17.9** | **Overall** | **93** | **16.0** |
| Developmental Delay | 37 | 6.4 | ADHD | 45 | 7.8 | GERD | 33 | 5.7 |
| Epilepsy | 24 | 4.1 | Anxiety | 24 | 4.1 | Constipation | 20 | 3.4 |
| Cerebral Palsy | 18 | 3.1 | Depression | 13 | 2.2 | Cow's Milk Protein Allergy | 8 | 1.4 |
| Autism Spectrum Disorder | 15 | 2.6 | Oppositional Defiant Disorder | 5 | 0.9 | Celiac Disease | 5 | 0.9 |
| Headache | 14 | 2.4 | Bipolar Disorder | 3 | 0.5 | Inflammatory Bowel Disease | 5 | 0.9 |
| Sleep Disorder | 10 | 1.7 | Mood Disorder | 3 | 0.5 | Cyclical Vomiting Syndrome | 2 | 0.3 |
| Hearing Loss | 4 | 0.7 | Obsessive Compulsive Disorder | 3 | 0.5 | Eosinophilic Esophagitis | 2 | 0.3 |
| Chiari Malformation | 3 | 0.5 | Adjustment Disorder | 1 | 0.2 | Necrotizing Enterocolitis | 2 | 0.3 |
| Hydrocephalus | 2 | 0.3 | Aggression | 1 | 0.2 | Omphalocele | 2 | 0.3 |
| Lennox-Gastaut Syndrome | 2 | 0.3 | Anorexia Nervosa | 1 | 0.2 | Abdominal Pain | 1 | 0.2 |

**Table 5.** Future Diagnoses of Patients with Elevated $B_{12}$ Levels

| **Psychiatry** | **N** | **%** | **Gastroenterology** | **N** | **%** | **Neurology** | **N** | **%** |
|---|---|---|---|---|---|---|---|---|
| **Overall** | **53** | **23.0** | **Overall** | **32** | **13.9** | **Overall** | **26** | **11.3** |
| ADHD | 15 | 6.5 | GERD | 7 | 3.0 | Headache | 7 | 3.0 |
| Depression | 13 | 5.7 | Constipation | 5 | 2.2 | Developmental Delay | 5 | 2.2 |
| Anxiety | 11 | 4.8 | Inflammatory Bowel Disease | 3 | 1.3 | Sleep Disorder | 3 | 1.3 |
| Bipolar Disorder | 3 | 1.3 | Dysphagia | 2 | 0.9 | Epilepsy | 2 | 0.9 |
| Obsessive Compulsive Disorder | 3 | 1.3 | Small Bowel Bacterial Overgrowth | 2 | 0.9 | Restless Leg Syndrome | 2 | 0.9 |
| Autism | 2 | 0.9 | Abdominal Pain | 1 | 0.4 | Chiari Malformation | 1 | 0.4 |
| Panic Attack | 2 | 0.9 | Autoimmune Hepatitis | 1 | 0.4 | Dysautonomia | 1 | 0.4 |
| Schizophrenia | 2 | 0.9 | Cyclical Vomiting Syndrome | 1 | 0.4 | Febrile Seizure | 1 | 0.4 |
| Trichotillomania | 1 | 0.4 | Delayed Gastric Emptying | 1 | 0.4 | Lennox-Gastaut Syndrome | 1 | 0.4 |
| Oppositional Defiant Disorder | 1 | 0.4 | Eosinophilic Esophagitis | 1 | 0.4 | Movement Disorder | 1 | 0.4 |

broad use of this test, it is important for pediatricians to understand its diagnostic implications, especially with unexpected results.

There are currently no pediatric guidelines for working up patients with elevated $B_{12}$ levels, leaving pediatricians without a codified approach to follow upon its discovery. Furthermore, the clinical conundrum of when to involve subspecialist physicians for abnormal results is an omnipresent challenge. Of our patients with elevated $B_{12}$ levels, 6.3% were referred to a hematology/oncology clinic for further management. However, despite the strong association between elevated vitamin $B_{12}$ and hematological and oncological diseases in adults, there are minimal studies to date that address these associations in the pediatric population, leaving hematology/oncology subspecialists with a high level of uncertainty in how to manage these patients and whether they should consider $B_{12}$ as an indicative or a predictive factor for a malignant process. Importantly, the results of our study indicate no clinical significance between elevated vitamin $B_{12}$ levels and pediatric malignancy. We report only one case of future malignancy among 384 total cases of elevated vitamin $B_{12}$ over a 5-year time period. Upon further chart review, this patient was diagnosed with LCH within four months of having the $B_{12}$ level drawn for an unknown indication. As such, our study suggests there may be no indication for further work up on the basis of an elevated vitamin $B_{12}$ beyond a one-year follow-up period and discovery of a future malignancy is unlikely after this time in the pediatric population. Supporting this, a large Danish study including patients of all ages, found that high plasma $B_{12}$ levels increased the risk of subsequently diagnosed cancer mostly within the first year of follow-up [10]. Although our study is not meant to be extrapolated to the general adult population, it may provide some relief for both general pediatricians and pediatric hematologists and oncologists.

In fact, it is worth highlighting that the most common associated prior medical problems in patients with elevated $B_{12}$ levels were found to be neuropsychiatric and gastroenterological in nature. It is well known that Vitamin $B_{12}$ is necessary for the development and initial myelination of the central nervous system as well as for the maintenance of its normal function [11]. It requires an adequate diet and functioning gut for absorption. Upon ingestion, Cbl undergoes binding and unbinding with various proteins and cofactors for proper absorption by the digestive tract. Intrinsic factor (IF) must attach to Cbl

to form a Cbl-IF complex that binds Cbl-IF receptors in the terminal ileum for absorption into circulation [1,12]. Its transport through the bloodstream and uptake by tissue requires transcobalamins (TCB) I, II, and III, which are part of the haptocorrin (HC) superfamily. TCB I and III bind ~80% of cobalamin circulating in the blood, while the other ~20% is bound to TCB II. TCB II is especially important for tissue and hepatic uptake of coblamain [2,13,14]. Holocobalamin is the metabolically active portion of vitamin $B_{12}$ bound to TCB II; it is delivered to all DNA synthesizing cells [2,12,15]. Severe disorders are observed in congenital deficiencies in TCB II, illustrating the vital role played by this protein, including developmental neuropsychiatric disorders [2,14,16]. In our study, ADHD was the most common neuropsychiatric disorder associated with an elevated $B_{12}$ level. Developmental delay, cerebral palsy, epilepsy and anxiety made up the remainder of the top five associated neuropsychiatric disorders. Several studies have documented an inverse relationship between $B_{12}$ levels and these diseases. Altun, *et al.* reported that $B_{12}$ levels were significantly lower in children with ADHD and a Turkish study by Unal, *et al.* thereafter correlated lower $B_{12}$ levels with psychosomatic symptoms and learning problems as reported by teachers [17,18]. Literature also reports low serum levels of $B_{12}$ and folate as well as high homocysteine levels possibly playing an important role in the etiopathogenesis of Autism Spectrum Disease and infantile spasms, a form of epilepsy [18-20].

At first glance, it seems that our study contradicts known literature; however, a deeper look at $B_{12}$ physiology suggests otherwise. It is currently considered that an increase in plasma levels of $B_{12}$ may be an indicator of a functional deficit with clinical consequences paradoxically similar to those of vitamin $B_{12}$ deficiency [2]. An increase in the binding of $B_{12}$ to HCs, secondary to an elevation in their plasma levels (especially for TCB I and III which are by far the majority), leads to a potential decline in its attachment to TCB II and therefore alters $B_{12}$ delivery to the cells. Thus, a functional deficit in vitamin $B_{12}$ with an increase in homocysteine or methylmalonic acid levels can occur, even though the initial anomaly in this instance is not a deficiency in vitamin $B_{12}$ [1,2]. This lends to question whether the finding of elevated $B_{12}$ levels are more secondary to their functional deficit, which per Andres, *et al.* can occur at any serum level [2]. Our study found that ADHD was also the most common neuropsychiatric disease diagnosed after an elevated $B_{12}$ levels and gastroenterology was the second most common subspecialty with future diagnoses. It is well known that constipation can manifest as a sign of $B_{12}$ deficiency and autoimmune disorders, including but not limited to, celiac disease, inflammatory bowel disease, and pernicious anemia pathophysiologically impede vitamin $B_{12}$ absorption [8]. Thus, if the diagnosis has not already been made and the patient exhibits any associated symptoms, it begs physicians to further question whether an abnormally high serum cobalamin level is a warning sign requiring exclusion of ADHD, other neuropsychiatric underlying pathologies or gastroenterological disorders rather than hematologic or oncologic diagnoses.

Our study sits on several strengths. The main strength is the large sample size of patients whose data we were able to investigate. An almost equal number of males and females also allows results of this study to be generalized to both genders. We were able to identify indications for sending a $B_{12}$ level in a large portion of our patient cohort, as well as obtain concurrent, past diagnoses and future diagnoses in vast majority of the patients. Inevitably, although some patients were lost to follow-up or their $B_{12}$ level was drawn in the year 2014 or thereafter (prior to full five-year surveillance), the average follow-up time period was 3.5 years. This is well beyond the time frame our study suggests for follow-up of an elevated $B_{12}$ level to exclude a possible associated malignancy.

Of the limitations, it was not possible to exclude all patients taking B-complex supplements, multivitamins, or herbal supplements as these are often overlooked by the parent or patient themselves and are not always spontaneously reported. However, all patients prescribed treatment dosing of either oral or parenteral $B_{12}$ were excluded from the study. As such, we can be relatively confident that the mechanism resulting in elevated vitamin $B_{12}$ was not secondary to excessive high dose patient ingestion and likely the result of an additional process. Additionally, this study relied on chart review of physician notes and physicians obtaining additional labs simultaneous to the $B_{12}$ level. An ESR level was not drawn for 82.0% of patients (n = 315 patients) and a CRP level was not drawn for 75.5% of patients (n = 290). Elevated levels of $B_{12}$ have been associated with an increase in 90-day mortality and markers of sepsis including Sequential Organ Failure Assessment (SOFA) score and CRP in adults [21-23]. While we found a very weak positive correlation of CRP and $B_{12}$ levels, given the small sample size of patients whose CRP results were available and the weak correlation, it is difficult to interpret these results unequivocally. Our very limited data suggests that an elevated vitamin $B_{12}$ level is not likely to be a marker of inflammation in the pediatric population. However, more robust studies are needed to better assess such an association or validate this point.

## Conclusion

Our study results did not demonstrate an association of elevated $B_{12}$ levels with malignancies in the pediatric population. Furthermore, it seems unlikely at this time that $B_{12}$ can serve as a predictor of development of pediatric malignancies prospectively. There was one patient in our study who had a malignancy diagnosed within a year of detecting the abnormal $B_{12}$ level; however, it is feasible to believe that these were occurrences which happened by chance, independently of each other and there was no clinical or statistical correlation. We believe that in order to answer the question of whether there may be an association of elevated $B_{12}$ levels and development of malignancies, prospective studies are needed with long term data for outcomes and more data points with laboratory evaluations. Based on the results of our study, it seems that routine hematology/oncology follow-up may not be warranted for management of elevated $B_{12}$ level. However, as seen in our study and reported in the literature, associations of abnormal $B_{12}$ levels with other non-hematological and oncological diseases are possible. It is worth mentioning the association we found of elevated $B_{12}$ levels and neuropsychiatric and gastroenterological diagnoses and elucidating further whether these were cases of unrecognized functional deficit of $B_{12.}$ We are hopeful that the findings of our study will be useful for pediatricians' daily practices in terms of referrals for evaluations by broader range of subspecialists and likewise useful for subspecialists when evaluating referrals for elevated $B_{12}$ levels.

## Authorship and Contributorship

Dr. Butala designed the study and the data collection instruments, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Teresczuk designed the data collection and instruments, collected data, and helped draft the initial manuscript. Dr. Malay carried out the initial analyses, generated descriptive statistics, and helped draft the initial manuscript. Dr. Pateva conceptualized and designed the study and the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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