

# Knowledge and Awareness of Primary Immunodeficiency in Primary Care: A Survey of Family Physicians

Selma YESILKAYA<sup>1</sup> , Gurgun Tugce VURAL SOLAK<sup>2</sup> , Nur SIMSEK YURT<sup>3</sup> , Erdinc YAVUZ<sup>4</sup> 

<sup>1</sup> Division of Immunology and Allergy, Samsun Training and Research Hospital, Samsun, Türkiye

<sup>2</sup> Division of Immunology and Allergy, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Türkiye

<sup>3</sup> Division of Family Medicine, Samsun Training and Research Hospital, Samsun, Türkiye

<sup>4</sup> Division of Family Medicine, Samsun University Faculty of Medicine, Samsun, Türkiye

Corresponding Author: Selma Yeşilkaya  selmayesilkaya@hotmail.com

## ABSTRACT

**Objective:** This study aimed to evaluate the awareness levels of family physicians regarding primary immunodeficiency (PID) and the adult “10 warning signs of PID” defined by international guidelines.

**Materials and Methods:** A descriptive, cross-sectional online survey was carried out between May 2025 and July 2025 among actively practicing family physicians. The questionnaire included 23 items addressing general knowledge of PID, awareness of the warning signs, and perceptions of related clinical features such as allergy, autoimmunity, malignancy, and autoinflammation.

**Results:** A total of 112 physicians participated. The mean age was  $42.48 \pm 8.14$  years, and the mean professional experience was  $17.46 \pm 8.51$  years; 66.1% were male. Most physicians correctly understood that recurrent infections are not the only finding of PID (92.0%) and that PID does not occur only in children (93.8%). However, only 21.4% of respondents had heard of the adult “10 warning signs.” Recognition rates for individual warning signs varied considerably, with high awareness for infections requiring prolonged antibiotics (85.7%) and unusual infections (84.8%), but lower recognition for recurrent pneumonias (47.3%) and chronic diarrhea with weight loss (58.0%). Understanding of PID-associated conditions was moderate, with 82.1% recognizing autoimmunity, 72.3% recognizing autoinflammation, and 61.6% recognizing both allergy and malignancy as potential PID manifestations. No significant differences in knowledge were found across demographic groups including age, gender, professional experience, or practice location.

**Conclusion:** Although family physicians demonstrated adequate general knowledge about PID, awareness of the adult “10 warning signs” remained limited. These findings highlight the urgent need for targeted educational interventions to improve early recognition and referral, which may ultimately enhance patient outcomes.

**Keywords:** Primary immunodeficiency, family physicians, awareness, warning signs, survey study

## INTRODUCTION

Primary immunodeficiencies (PIDs), currently also referred to as inborn errors of immunity (IEI), represent a heterogeneous group of genetic disorders that impair the development or function of the immune system. These conditions predispose patients not only to recurrent infections but also to autoimmunity, inflammation, allergies, and malignancies (1). According to the most recent 2024 update of the International Union of Immunological Societies (IUIS) Expert Committee, 559 distinct PIDs have been identified, reflecting substantial growth from 485

disorders documented in 2022, and this number continues to expand annually (2).

Although individually rare, PIDs collectively are more common than generally perceived and represent a substantial public health burden. It is estimated that in the United States, approximately 1 in 1200 individuals may be affected by PID (3). The European Society for Immunodeficiencies (ESID) has established a registry system to facilitate the long-term follow-up of patients and improve the diagnosis, prognosis, and treatment of PIDs (4).

ORCID  Selma Yesilkaya / 0000-0002-1841-0177, Gurgun Tugce Vural Solak / 0000-0003-3890-9255, Nur Simsek Yurt / 0000-0000-6585-9663, Erdinc Yavuz / 0000-0002-3275-8399

Despite this, early and accurate diagnosis of PID is often delayed due to limited awareness and diagnostic challenges worldwide, leaving many patients undiagnosed, misdiagnosed, or diagnosed late. Studies show that the mean diagnostic delay is 4.08 years globally (5), while in Finland the average delay in diagnosing common variable immunodeficiency (CVID) was reported as 8 years (6, 7). Such delays negatively affect the quality of life, contributing to severe complications, irreversible organ damage, and even death. Family physicians serve as the first point of contact in healthcare systems, making them critically positioned to recognize early warning signs and initiate timely referrals. Enhanced awareness at the primary care level is therefore essential to reducing diagnostic delays and improving patient outcomes.

To facilitate early recognition, the Jeffrey Modell Foundation (JMF) developed the “10 Warning Signs of PID” for both children and adults (8). The presence of any of these signs should prompt suspicion of PID. These include  $\geq 4$  antibiotic-requiring infections within a year, recurrent or persistent infections resistant to treatment,  $\geq 2$  serious bacterial infections,  $\geq 2$  radiologically confirmed pneumonias in 3 years, chronic diarrhea with weight loss, infections with unusual pathogens or at atypical sites, recurrent unexplained fevers, deep-seated abscesses, persistent oral candidiasis without recent antibiotics, and a positive family history of PID. Although criticized for not fully capturing the expanding spectrum of PID manifestations, particularly autoimmunity and malignancy, familiarity with these signs has been shown to enhance physicians’ recognition of related clinical conditions.

However, several studies have demonstrated low awareness of PID among physicians, especially in primary care. For example, a Brazilian study reported that 77% of physicians were unfamiliar with the warning signs of PID, and only a minority of specialists could correctly identify most related clinical scenarios (9). Previous surveys conducted among physicians from various specialties have revealed substantial knowledge gaps in the recognition and management of PID. However, most of these studies have primarily focused on specialists. Considering the pivotal role of primary care in early diagnosis, evaluating family physicians’ knowledge and awareness of PID represents an important yet underexplored area. In this context, assessing the knowledge and experience of primary care physicians in our region of Turkiye is essential for developing strategies to enhance awareness and improve the early detection of these rare disorders.

This study aimed to evaluate the knowledge and awareness of family physicians regarding PID and the ‘10 warning signs,’ with a focus on their role in early recognition and referral.

## MATERIALS and METHODS

This study was conducted as a descriptive, cross-sectional survey. According to data from Samsun Provincial Health Directorate, there are 453 family physicians in the province. A total of 112 family physicians (24.7%) participated in the study.

Ethical approval was obtained from the Samsun University Non-Clinical Research Ethics Committee (Decision No: 2025/8/20, Date: 16 April 2025). Following ethical approval, permission was also secured from the Samsun Provincial Health Directorate’s Research and Development Department (Reference No: E-79222180-604.01-276999430). The Directorate officially notified all family medicine practices within the province about the study and provided approval for data collection. All procedures were carried out in accordance with the principles of Good Clinical Practice Guidelines and the Declaration of Helsinki. The survey was administered online to family physicians practicing in Samsun province between May 2025 and July 2025. The survey link was distributed through official family medicine professional groups and email lists. Two reminder messages were sent at two-week intervals to maximize response rates. At the beginning of the questionnaire, participants were required to provide informed consent electronically. The study population consisted of all actively practicing family physicians in the province (n=453). A total of 112 family physicians responded, yielding a response rate of 24.7%.

The inclusion criteria were: (1) currently practicing as a family physician and (2) voluntary participation. The sole exclusion criterion was refusal to participate.

The questionnaire was developed by the researchers based on a comprehensive literature review and previously published tools (8,9). It comprised 23 items, including both open-ended and closed-ended questions, with response options of “yes,” “no,” or “I don’t know.” The questionnaire items were directly adapted from the Jeffrey Modell Foundation’s 10 warning signs and validated questions from previous studies on PID awareness among physicians (1,8,9). Although formal pilot testing was not conducted, the questionnaire underwent expert review by two immunology specialists to ensure content validity and

clinical relevance. The questionnaire consisted of 23 questions structured as follows:

- Questions 1-6: Demographic characteristics (age, gender, years of professional experience, working area, graduation year, specialization status)
- Questions 7-9: PID awareness and knowledge level (familiarity with PID, information sources, previous experience diagnosing PID)
- Questions 10-19: Knowledge about the 10 warning signs of PID
- Questions 20-23: PID-associated clinical conditions (autoimmunity, allergy, malignancy, and autoinflammation)

### Statistical Analysis

All analyses were conducted using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the histograms and Q-Q plots. Continuous variables (e.g., age, years of professional experience, registered population size) were presented as mean  $\pm$  standard deviation (SD) or median (quartiles) values depending on the normality of data distribution. Categorical variables (e.g., gender, professional title, practice location) are expressed as frequencies and percentages. Between-groups analysis of answers were performed using chi-square test or Fisher's exact test or Fisher-Freeman-Halton test. Total numbers of correct answers were analyzed using the Mann Whitney U test or Kruskal Wallis test depending on the count of the groups, as the data did not conform to a normal distribution. A p-value of  $<0.05$  was considered statistically significant.

### RESULTS

A total of 112 family physicians participated in this study. Table I presents the demographic characteristics of participants. The majority were male (66.07%, n=74), with a mean age of  $42.48 \pm 8.14$  years. The mean professional experience was  $17.46 \pm 8.51$  years. In terms of practice location, 61.61% (n=69) worked in urban centers while 38.39% (n=43) practiced in rural areas.

Only 21.43% of the participants had heard of the 10 warning signs of PID for adults. However, the majority correctly identified that recurrent infections are not the only finding of PID (91.96%) and that PID does not occur

exclusively in children (93.75%). Recognition rates for individual PID warning signs varied considerably. High recognition was observed for infections requiring prolonged intravenous antibiotics (85.71%), infections with unusual pathogens or unusual localization (84.82%), serious bacterial infections (80.36%), recurrent deep abscesses (82.14%), recurrent unexplained fever (80.36%), and persistent oral thrush (75.89%). In contrast, lower recognition rates were noted for radiologically confirmed pneumonias (47.32%) and chronic diarrhea with weight loss (58.04%). Regarding PID-associated conditions, 82.14% of participants recognized autoimmunity, 72.32% recognized autoinflammation, and 61.61% recognized both allergy and malignancy as potential manifestations of PID (Table II).

Notably, the proportion of "I don't know" responses varied substantially across different warning signs. While uncertainty was relatively low for well-recognized infectious symptoms such as prolonged antibiotic requirements (8.93%) and unusual infections (11.61%), considerably higher "I don't know" rates were observed for less specific manifestations. Specifically, 37.50% of participants were uncertain about radiologically confirmed recurrent pneumonias, and 29.46% were uncertain about chronic diarrhea with weight loss as warning signs. Similarly, for PID-associated conditions, "I don't know" responses constituted 27.68% for allergy, 25.00% for autoinflammation, 21.43% for malignancy, and 16.07% for autoimmunity.

**Table I: General Characteristics of the Participants**

Characteristics	Descriptive statistics
Age, years, mean $\pm$ SD	$42.48 \pm 8.14$
Gender, Male, n (%)	74 (66.07)
Years of Professional Experience, mean $\pm$ SD	$17.46 \pm 8.51$
Professional Title in Family Medicine, n (%)	
General Practitioner in Family Medicine	32 (28.57)
Contracted Family Medicine Resident (SAHU)	65 (58.04)
Specialist in Family Medicine	15 (13.39)
Registered Population per Physician, median (quartiles)	3002.5 (2500-3420)
Practice Location, n (%)	
Rural Area	43 (38.39)
Urban Center	69 (61.61)

**SD:** Standard deviation, **SAHU:** "Sözleşmeli Aile Hekimliği Uzmanlık Öğrencisi" a contract training program for family medicine specialization in Türkiye.

**Table II: Distribution of Participants' Responses to Primary Immunodeficiency Knowledge Questions**

Questions	Descriptive statistics	Questions	Descriptive statistics
Have heard of the 10 warning signs of PID for adults, n (%)		Recurrent unexplained fever, n (%)	
Yes	24 (21.43)	True	90 (80.36)
No	88 (78.57)	False	11 (9.82)
Recurrent infections are the only finding of PID, n (%)		I don't know	11 (9.82)
True	9 (8.04)	Recurrent deep abscesses, n (%)	
False	103 (91.96)	True	92 (82.14)
I don't know	0 (0.00)	False	5 (4.46)
PID occurs only in children, n (%)		I don't know	15 (13.39)
True	7 (6.25)	Persistent oral thrush, n (%)	
False	105 (93.75)	True	85 (75.89)
I don't know	0 (0.00)	False	11 (9.82)
≥4 infections per year (sinusitis, bronchitis, otitis media, etc.), n (%)		I don't know	16 (14.29)
True	76 (67.86)	Family history of PID, n (%)	
False	7 (6.25)	True	89 (79.46)
I don't know	29 (25.89)	False	6 (5.36)
Infections requiring prolonged/IV antibiotics, n (%)		I don't know	17 (15.18)
True	96 (85.71)	Autoimmunity, n (%)	
False	6 (5.36)	True	92 (82.14)
I don't know	10 (8.93)	False	2 (1.79)
≥2 serious bacterial infections (osteomyelitis, septic arthritis, etc.), n (%)		I don't know	18 (16.07)
True	90 (80.36)	Allergy, n (%)	
False	6 (5.36)	True	69 (61.61)
I don't know	16 (14.29)	False	12 (10.71)
≥2 radiologically confirmed pneumonias in 3 years, n (%)		I don't know	31 (27.68)
True	53 (47.32)	Malignancy, n (%)	
False	17 (15.18)	True	69 (61.61)
I don't know	42 (37.50)	False	19 (16.96)
Chronic diarrhea with weight loss, n (%)		I don't know	24 (21.43)
True	65 (58.04)	Autoinflammation, n (%)	
False	14 (12.50)	True	81 (72.32)
I don't know	33 (29.46)	False	3 (2.68)
Infection with unusual localization/pathogen, n (%)		I don't know	28 (25.00)
True	95 (84.82)	For percentage data, bold the entire row that represents the correct response	
False	4 (3.57)		
I don't know	13 (11.61)		

These patterns suggest that while family physicians recognize classic infectious presentations, substantial uncertainty exists regarding non-infectious and atypical manifestations of PID.

Physicians with <15 years of professional experience demonstrated slightly higher awareness of the 10 warning signs compared to those with ≥15 years of experience (25.58% vs 18.84%); however, this difference was not sta-

tistically significant ( $p=0.543$ ). Both experience groups demonstrated similar correct response rates across all PID knowledge questions, with no statistically significant differences observed (all  $p$ -values  $>0.05$ ) (Table III).

The overall median score of correct answers was 13 out of 15 PID knowledge questions (IQR: 10-15). No statistically significant differences in total correct answers were observed across any demographic characteristics, including age (<40 vs  $\geq 40$  years: median 12 vs 13,  $p=0.956$ ), gender (male vs female: median 12 vs 13.5,  $p=0.322$ ), years of professional experience (<15 vs  $\geq 15$  years: median 12 vs 13,  $p=0.887$ ), professional title ( $p=0.776$ ), registered population size ( $p=0.385$ ), or practice location (rural vs urban: both median 13,  $p=0.571$ ) (Table IV).

## DISCUSSION

This study assessed family physicians' knowledge of PID, the 10 warning signs, and PID-associated conditions

including allergy, autoimmunity, malignancy, and autoinflammation. Overall, physicians showed good basic knowledge (e.g., rejecting that PID occurs only in children), but awareness of specific warning signs and associated conditions like malignancy or chronic diarrhea was much lower.

Awareness and adequate knowledge of immunodeficiency are critical components in the diagnosis of PID. However, studies evaluating physicians' and medical students' knowledge, attitudes, and awareness of PID remain scarce. For instance, a study conducted at a pediatric center in Peru reported that only 39.8% of physicians were familiar with the 10 warning signs, and 57.7% cited limited access to laboratory tests as the major barrier to diagnosis (10). Similarly only 21.4% of participants were aware of the 10 warning signs. As this survey was conducted among primary care physicians, their knowledge of laboratory testing and treatment practices was not evaluated. Previous studies in Türkiye have also documented limited

**Table III: Distribution of Participants' Responses to Primary Immunodeficiency Knowledge Questions With Regard to Years of Professional Experience**

Questions	Years of Professional Experience		p
	<15 (n=43)	$\geq 15$ (n=69)	
Have heard of the 10 warning signs of PID for adults, n (%)			
Yes	11 (25.58)	13 (18.84)	0.543 <sup>†</sup>
No	32 (74.42)	56 (81.16)	
Correct Answer to...			
Recurrent infections are the only finding of PID, n (%)	42 (97.67)	61 (88.41)	0.150 <sup>‡</sup>
PID occurs only in children, n (%)	42 (97.67)	63 (91.30)	0.247 <sup>‡</sup>
$\geq 4$ infections per year (sinusitis, bronchitis, otitis media, etc.), n (%)	30 (69.77)	46 (66.67)	0.894 <sup>‡</sup>
Infections requiring prolonged/IV antibiotics, n (%)	36 (83.72)	60 (86.96)	0.843 <sup>‡</sup>
$\geq 2$ serious bacterial infections (osteomyelitis, septic arthritis, etc.), n (%)	34 (79.07)	56 (81.16)	0.979 <sup>‡</sup>
$\geq 2$ radiologically confirmed pneumonias in 3 years, n (%)	22 (51.16)	31 (44.93)	0.654 <sup>‡</sup>
Chronic diarrhea with weight loss, n (%)	24 (55.81)	41 (59.42)	0.858 <sup>‡</sup>
Infection with unusual localization/pathogen, n (%)	36 (83.72)	59 (85.51)	1.000 <sup>‡</sup>
Recurrent unexplained fever, n (%)	33 (76.74)	57 (82.61)	0.606 <sup>‡</sup>
Recurrent deep abscesses, n (%)	37 (86.05)	55 (79.71)	0.550 <sup>‡</sup>
Persistent oral thrush, n (%)	34 (79.07)	51 (73.91)	0.694 <sup>‡</sup>
Family history of PID, n (%)	36 (83.72)	53 (76.81)	0.522 <sup>‡</sup>
Autoimmunity, n (%)	34 (79.07)	58 (84.06)	0.677 <sup>‡</sup>
Allergy, n (%)	29 (67.44)	40 (57.97)	0.422 <sup>‡</sup>
Malignancy, n (%)	27 (62.79)	42 (60.87)	0.997 <sup>‡</sup>
Autoinflammation, n (%)	31 (72.09)	50 (72.46)	1.000 <sup>‡</sup>

<sup>†</sup> Chi-square test, <sup>‡</sup> Fisher's exact test.

**Table IV: Total Numbers of Correct Answers With Regard to General Characteristics of the Participants**

Characteristics	n	Total Numbers of Correct Answers, median (quartiles)	p
Overall	112	13 (10 - 15)	-
Age, years			
<40	40	12 (10.5 - 15)	0.956 <sup>†</sup>
≥40	72	13 (10 - 15)	
Gender			
Male	74	12 (10 - 15)	0.322 <sup>†</sup>
Female	38	13.5 (11 - 15)	
Years of Professional Experience			
<15	43	12 (10 - 15)	0.887 <sup>†</sup>
≥15	69	13 (10 - 15)	
Professional Title in Family Medicine			
General Practitioner in Family Medicine	32	12 (10 - 14.5)	0.776 <sup>‡</sup>
Contracted Family Medicine Resident (SAHU)	65	13 (10 - 15)	
Specialist in Family Medicine	15	12 (9 - 15)	
Registered Population per Physician			
<3000	50	13 (11 - 15)	0.385 <sup>†</sup>
≥3000	62	12.5 (10 - 14)	
Practice Location			
Rural Area	43	13 (10 - 15)	0.571 <sup>†</sup>
Urban Center	69	13 (10 - 15)	

**SAHU:** “Sözleşmeli Aile Hekimliği Uzmanlık Öğrencisi” a contract training program for family medicine specialization in Türkiye.

† Mann Whitney U test, ‡ Kruskal Wallis test.

awareness of PID. A survey conducted by Yüksek et al. (11) over a decade ago, conducted exclusively with pediatricians, questioned clinical and laboratory findings, and found low awareness. However, the 10 warning signs were not addressed. More recently, Esenboğa et al. (12) reported a lack of awareness and knowledge among specialists from various specialties, including pediatricians, family physicians, internal sciences, and surgical sciences. Family physicians comprised only 11% of the total participants in the study, and the survey questions also asked about diagnosis and treatment. These studies primarily included hospital-based physicians and specialists. Our study specifically targeted family physicians, who serve as primary gatekeepers in the healthcare system and are often the first point of contact for patients. This focus is critical because family physicians have the earliest opportunity to recognize and address warning signs, yet their awareness has not been adequately studied in Türkiye. Our findings suggest that despite adequate basic understanding of PID, specific knowledge of warning signs and noninfectious

manifestations remains limited among family physicians and that previous educational efforts have not adequately reached primary care practitioners.

In a survey assessing medical students' awareness of PID and their knowledge of the 10 warning signs in both adults and children, the mean percentage of correct responses per question was  $59.2 \pm 10.9\%$ . Based on these findings, it was concluded that PID awareness among medical students is low and requires improvement through targeted education (8). A study conducted by Imai et al. in Japan included 355 physicians, comprising 121 pediatricians, 116 hematologists, and 118 general internists. Awareness levels varied by specialty and were reported as 52%, 47.4%, and 33.1%, respectively. The study evaluated recognition of PID across four clinical scenarios: (1) presenting with current disease complaints at the initial visit; (2) adding information about previous infection history; (3) including gastroenterological symptoms in the medical history; and (4) providing a positive family history. The likelihood

of suspecting PID increased in line with the amount of information provided, rising progressively to 30.4%, 73.8%, 77.2%, and 83.4%. Furthermore, regarding the 10 warning signs of PID in adults, more than half of the physicians (62.5%) reported lacking sufficient experience and knowledge for diagnosis and acknowledged being unaware of these warning signs (1). Primary care physicians demonstrated high correct response rates for infections requiring prolonged antibiotics (85.7%) and unusual infections (84.8%), yet 78.6% were unaware of the formal 10 warning signs framework. Interestingly, physicians showed stronger knowledge of infection-related warning signs compared to non-infectious manifestations. While 85.7% recognized prolonged antibiotic requirements and 84.8% identified unusual infections, only 47.3% recognized recurrent pneumonias and 58.0% identified chronic diarrhea with weight loss. This pattern suggests that family physicians have a better understanding of the infectious aspects of PID but struggle with recognizing less obvious presentations. Several factors may explain this discrepancy. First, family medicine training traditionally emphasizes infectious diseases and acute care, with less focus on complex immunological disorders and their protean manifestations. Second, non-infectious presentations such as chronic diarrhea, recurrent pneumonias, and malignancy develop insidiously and may be attributed to more common conditions in primary care settings, leading to anchoring bias. Third, the low prevalence of PID means that most family physicians encounter few, if any, cases during their careers, limiting experiential learning opportunities. Fourth, the evolving classification of inborn errors of immunity, which now encompasses a broader spectrum of immune dysregulation beyond recurrent infections, may not have been adequately disseminated to primary care practitioners. Finally, the absence of structured screening protocols or clinical decision support tools in primary care settings means that recognition relies heavily on individual physician knowledge rather than systematic approaches.

Eldeniz et al. (9) evaluated the applicability of the 10 warning signs in secondary immunodeficiency (SID). They concluded that although these signs may be useful in the early detection of SID, modifications are necessary for the early diagnosis of PID. Their findings highlighted chronic diarrhea, tuberculosis, rheumatic diseases, malignancy, and family history as statistically significant predictors of PID, and further suggested that autoimmune diseases and malignancies should also be emphasized as warning signs (9). In line with this, this study showed that

58% of respondents correctly identified chronic diarrhea with weight loss as a sign of PID, while 29.5% selected "I don't know". Malignancy represents a significant non-infectious manifestation of PID, with hematological cancers occurring more frequently than solid tumors. Recent comprehensive data from the European Society for Immunodeficiencies (ESID) registry spanning three decades (1994-2024) and encompassing over 30,000 patients provides robust evidence that malignancy is a substantial concern in PID populations, reinforcing the importance of recognizing this association (13). While 61.6% correctly recognized malignancy as a PID manifestation, 21.4% were uncertain, highlighting a knowledge gap. Hariyan T. and colleagues conducted a longitudinal survey between 2016 and 2019 to assess physicians' knowledge of PID diagnosis, warning signs, treatment, vaccination, and the most common PID-related diseases in their regions. The study compared responses from 82 physicians in 2016 with those of 67 physicians in 2019, including pediatricians, general practitioners/family physicians, and pediatric subspecialists. Following the initial survey, targeted educational interventions—such as workshops and seminars addressing early diagnosis, laboratory evaluation, and treatment—were implemented over a two-year period. After these training activities, the proportion of correct responses increased by more than 20% across all survey items (14). A survey conducted among primary care physicians in the United States reported that only 32% had diagnosed, treated, or referred a patient with PID within the past five years, underscoring the need for additional physician training (15). Similarly, in a large-scale survey by Dantas et al. involving 4,026 physicians (40.4% pediatricians, 35.7% internists, and 23.9% surgeons), 84% reported evaluating patients with frequent antibiotic use, yet only 40.3% indicated that they had participated in the immunological assessment of such patients (6).

PID present with a broad spectrum of clinical manifestations. Noninfectious features are relatively uncommon compared to infectious presentations and are also less frequently recognized. Primary Immune Regulatory Disorders (PIRDs) represent a notable subgroup of PID (16). In a large study evaluating the initial presentation of 16,486 patients with PID, 68% presented with infection, 9% with immune dysregulation, and 9% with a combination of both (17). These diverse clinical manifestations contribute to frequent delays in diagnosis. In this study, although the correct response rates for infection-related questions were high, 37.5% of participants responded "I

don't know" to the item " $\geq 2$  radiologically confirmed pneumonias in 3 years." It is concerning that fewer than half of the physicians recognized recurrent pneumonia as a warning sign, even though it is among the classic indicators of PID. Similarly, a French study investigating the prevalence of autoimmune and inflammatory manifestations in PID evaluated 2,183 patients. At least one autoimmune or inflammatory condition was identified in 571 patients (26.2%), most commonly autoimmune cytopenias, followed by gastroenterological disorders, dermatologic conditions, rheumatologic diseases, endocrine disorders, and pulmonary or ocular involvement (18). In this study, the proportions of participants who responded "I don't know" regarding the association of autoimmunity and autoinflammation with PID were 16.1% and 25%, respectively. In this study, 69 physicians (61.6%) correctly identified allergy as a potential indicator of PID, whereas 31 physicians (27.7%) responded "I don't know." The skin is among the organs that may be affected in PID, and dermatological manifestations such as dermatitis, petechiae, and vasculitis can provide important diagnostic clues. Cutaneous complications may also include infections, abscesses, and skin cancers. Aghamohammadi et al. investigated the prevalence of PID in patients with severe atopic dermatitis and reported that 5 of 75 patients (6.6%) were diagnosed with Hyper IgE Syndrome (HIES), while 1 patient (1.3%) was diagnosed with Wiskott–Aldrich Syndrome (WAS) (19). These findings suggest that the recognition of PID warning signs beyond recurrent infections remains limited.

The reasons for this gap include the wide genetic and phenotypic heterogeneity of the disease and the continual identification of new genetic variants, the insufficient emphasis on PID during medical school and residency training, the tendency for physicians to become distanced from ongoing education and recent developments as their years in practice increase (despite newer graduates demonstrating greater knowledge and awareness), and the limited availability of diagnostic laboratory facilities. Knowledge gaps were consistent across all demographic subgroups, suggesting that the problem is widespread and not confined to a particular group of physicians. Even specialization status did not lead to better awareness, underlining the need for structured educational programs at all levels.

This study has several limitations that should be considered when interpreting the results. First, we only surveyed family physicians in Samsun province, which may

limit the generalizability of our findings to other regions or healthcare systems. Second, the response rate was 24.7%, which could introduce selection bias if physicians with different knowledge levels were more or less likely to participate. Third, we used a self-report questionnaire format, which may not fully capture actual clinical decision-making skills when evaluating patients with suspected PID. Fourth, this study design was cross-sectional, so we cannot determine whether knowledge levels change over time or assess the impact of educational interventions. Fifth, we did not evaluate participants' access to immunology specialists or diagnostic facilities, which could influence their confidence in recognizing PID symptoms. Sixth, although the questionnaire was based on established tools and underwent expert review, formal psychometric validation including reliability and validity testing was not conducted, which may affect the precision of our measurements. Finally, the study focused on awareness and knowledge rather than actual diagnostic practices, so the relationship between knowledge and patient outcomes remains unclear. Despite these limitations, our findings provide valuable insights into current PID awareness among family physicians and highlight areas for targeted educational improvement.

The findings of this study have important implications for medical education and continuing professional development. First, undergraduate medical curricula should incorporate more comprehensive coverage of PID, emphasizing not only infectious manifestations but also non-infectious presentations such as autoimmunity, chronic diarrhea, and malignancy. Second, targeted educational interventions for practicing family physicians are urgently needed. These could include structured continuing medical education (CME) modules focused on PID recognition, integration of PID warning signs into clinical decision support systems, and periodic refresher workshops conducted by immunology specialists. Our recent experience delivering a seminar on approach to PIDs to family medicine residents and practicing family physicians demonstrated strong engagement and identified specific knowledge gaps that can guide future educational content. Third, national primary care guidelines should explicitly incorporate screening protocols for PID, providing family physicians with clear algorithms for when to suspect PID and how to initiate referrals. Fourth, collaboration between immunology specialists and family medicine departments could facilitate case-based learning and mentorship programs. Finally, awareness campaigns targeting

both healthcare professionals and the general public may help increase recognition and reduce the stigma associated with immunodeficiency disorders. Implementing these strategies could significantly reduce diagnostic delays and improve outcomes for patients with PID.

## CONCLUSION

This study demonstrated that while family physicians possess adequate basic knowledge of PID, their awareness of the 10 warning signs remains limited, particularly for non-infectious manifestations. These findings call for immediate action through several evidence-based strategies: development of targeted CME modules specifically addressing PID recognition in primary care, integration of PID screening protocols into national family medicine guidelines, implementation of clinical decision support systems to prompt consideration of PID in relevant clinical scenarios, and establishment of collaborative educational programs between immunology specialists and primary care practitioners. Additionally, periodic refresher training emphasizing the evolving spectrum of PID beyond recurrent infections is essential. By implementing these targeted interventions, we can enhance early recognition capabilities among family physicians, reduce diagnostic delays, and ultimately improve outcomes for patients with PID.

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### Consent

The questionnaire is adapted for online consent as a converter for family doctors working in Samsun.

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### Ethics Committee Approval

Ethical approval was obtained from the Samsun University Non-Clinical Research Ethics Committee (Decision No: 2025/8/20, Date: 16 April 2025). All procedures were carried out in accordance with the principles of the Good Clinical Practice Guidelines and the Declaration of Helsinki.

### Conflict of Interest

The authors have no competing interests to declare.

### Author Contributions

Concept: Selma Yesilkaya, Gurgun Tugce Vural Solak, Design: Gurgun Tugce Vural Solak, Data Collection and/or Processing: Selma Yesilkaya, Gurgun Tugce Vural Solak, Nur Simsek Yurt, Erdinc Yavuz, Analysis and/or Interpretation: Selma Yesilkaya, Nur Simsek Yurt, Gurgun Tugce Vural Solak, Erdinc Yavuz; Literature Review: Selma Yesilkaya; Writing: Selma Yesilkaya, Gurgun Tugce Vural Solak, Approval: All authors.

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