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Inborn Errors of Immunity Awareness among Physicians: Multicenter Data from Türkiye



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Abstract

Objective: To assess the awareness, diagnostic approach, and perceived barriers related to inborn errors of immunity (IEIs) among physicians caring for pediatric patients in Türkiye.

Methods: In this cross-sectional online survey (July–October 2025), 488 physicians completed a 44-item questionnaire covering ten domains, including demographics, IEI-related education, recognition of clinical warning signs, use of immunologic tests, referral patterns, and perceived barriers. Participants comprised pediatric specialists, pediatric residents, pediatric subspecialty fellows/attending, family medicine specialists/residents, and general practitioners. Descriptive statistics were calculated, and group comparisons were performed using the chi-square test ($p < 0.05$).

Results: The mean age of participants was 33.7 ± 6.5 years; 61.9% worked in university or training and research hospitals. Overall, 63.5% had previously evaluated a child with IEI, but independent diagnosis was mainly confined to pediatric subspecialists (57.4%) and pediatricians (47.4%), and was rare among family physicians and general practitioners (3–6%). Recognition of IEI-associated clinical features showed a clear specialty gradient: pediatric subspecialists consistently achieved the highest scores across infectious, autoimmune/inflammatory, dermatologic, neurological/syndromic, and growth/genetic domains, whereas family physicians and general practitioners demonstrated significantly lower recognition ($p < 0.001$ across domains). Only 52.7% of physicians had heard of the Jeffrey Modell warning signs; however, 82% expressed their willingness to receive further IEI-focused education. Major reported barriers included limited laboratory capacity, insufficient training, difficult access to immunology specialists, and complex referral pathways.

Conclusion: Substantial gaps in IEI knowledge and diagnostic practices exist, particularly in non-infectious domains and among primary care physicians in Türkiye. Targeted educational programs, improved access to immunologic testing, and streamlined referral pathways are urgently needed to facilitate earlier recognition and better outcomes for children with suspected IEI.

Keywords

Inborn errors of immunity • Primary immunodeficiency • Clinical decision-making • Physician awareness • Diagnostic delays



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INTRODUCTION

IEIs are a broad group of disorders resulting from genetic defects in the immune system, leading to increased susceptibility to infections, autoimmunity, autoinflammation, and malignancy. Formerly referred to as IEI, these conditions are now recognized as a multidimensional clinical spectrum reflecting the complex genetic basis of the human immune system. According to the 2024 report of the International Union of Immunological Societies (IUIS) Expert Committee, a total of 508 genes and 17 phenocopies have been associated with IEIs, substantially expanding our understanding of human immune regulation and disease mechanisms (1).

Although the reported incidence varies by region, recent population-based data estimate the prevalence of IEIs to be approximately 6 per 10,000 individuals (≈ 1 in 1,600), indicating that these disorders are not rare (1).

In Turkey, the true prevalence of IEIs remains uncertain due to the absence of a national registry system. However, the high rate of consanguineous marriages contributes to a relatively increased frequency of autosomal recessive forms of immunodeficiency. Family physicians, general practitioners, pediatricians, and pediatric subspecialists who care for children at various levels of the healthcare system frequently encounter patients presenting with recurrent or treatment-resistant infections, growth failure, or unusual clinical manifestations, which may indicate an underlying immune defect (2).

Early diagnosis is one of the most critical determinants of the clinical course in inborn errors of immunity (IEIs). Simple screening tests such as complete blood count, lymphocyte subset analysis, and measurement of serum immunoglobulin levels provide essential diagnostic clues for many cases and represent the first step toward recognition (3). However, when these initial evaluations are inconclusive, more advanced immunological investigations or genetic analyses are required. Establishing the diagnosis before the onset of severe infections or irreversible organ damage markedly reduces both morbidity and mortality (4).

Nevertheless, limited awareness of IEIs among primary care physicians and pediatric specialists may lead to diagnostic delays, unnecessary investigations, or inappropriate referrals. Therefore, improving physicians' knowledge and awareness regarding congenital immunodeficiencies is crucial for achieving early diagnosis and optimal treatment outcomes (2).

The aim of this study was to evaluate the level of awareness regarding inborn errors of immunity (IEIs) among physicians who frequently encounter pediatric patients including family physicians, general practitioners, pediatricians, and pediatric subspecialists

and to identify the clinical and laboratory indicators that facilitate accurate diagnosis.

MATERIALS AND METHODS

A cross-sectional survey was conducted between July and October 2025 to assess the awareness of healthcare professionals regarding IEIs. The questionnaire consisted of 43 closed-ended questions (some containing multiple sub-items) and 1 open-ended question. It was distributed to pediatric specialists, pediatric residents, family medicine specialists, family medicine residents, and pediatric subspecialists/fellows other than pediatric allergy and immunology. A total of 488 completed questionnaires were collected and included in the analysis.

The questionnaire was structured into 10 main domains to facilitate descriptive and analytical evaluation: demographic and professional information (6 items), clinical experience and patient load (3 items), education and awareness (4 items), management needs in IEIs (4 items), knowledge and attitudes toward IEIs (9 items), warning signs and clinical associations (4 items), lymphocyte count and laboratory knowledge (4 items), diagnostic approaches (1 item), challenges in immunological evaluation (1 item), and open-ended feedback (1 item).

The survey was administered online through digital platforms and professional communication groups, and participation was entirely voluntary. The questionnaire was developed based on an extensive review of the literature and current IEI diagnostic guidelines. Ethical approval for the study was obtained from the from the *Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee* (Approval No: 3052 Date: 17/06/2025). This study was conducted following the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the SPSS software for Windows. Descriptive statistics for categorical variables are presented as frequencies and percentages. Group comparisons of proportions were conducted using the chi-square test. A p-value of <0.05 was considered statistically significant.



RESULTS

Participant Characteristics

Table 1. Demographic and baseline professional characteristics of the participants

Variable	n (%)
Age, mean $\pm$ SD (min–max)	33.7 $\pm$ 6.5 (23–61)
Sex	
Male	153 (31.4)
Female	335 (68.6)
Specialty	
Family Medicine Resident	51 (10.5)
Family Medicine Specialist	63 (12.9)
Pediatrics Resident	94 (19.3)
Pediatrics Specialist	114 (23.4)
Other Pediatric Subspecialty Residency	37 (7.6)
Other Pediatric Subspecialty Specialist	54 (11.1)
General Practitioner	75 (15.4)
Years in active clinical practice	
< 1 year	48 (9.8)
1–5 years	162 (33.2)
6–10 years	146 (29.9)
>10 years	132 (27.0)
Institution type	
Private hospital / clinic	32 (6.6)
Training & Research / University Hospital	302 (61.9)
Family Medicine Center/Community Health Center	96 (19.7)
State hospital (secondary care)	51 (10.5)
Other	7 (1.4)
Pediatric patients evaluated per month (n = 423)	
0–50	96 (22.7)
51–100	45 (10.6)
101–200	41 (9.7)
>200	241 (57.0)

Continuous variables (age) are presented as mean $\pm$ SD (range), and categorical variables are expressed as number (percentage). Pediatric patient volume reflects responses from participants who actively evaluate children in their clinical practice (n = 423).

A total of 488 physicians participated in the study. The mean age of the participants was 33.7 $\pm$ 6.5 years (range: 23–61 years). The distribution across specialties was diverse, with pediatric specialists (23.4%), pediatric residents (19.3%), pediatric subspecialty fellows/attendings (18.7%), family medicine specialists/residents (23.4% combined), and general practitioners (15.4%).

Most participants were employed in training and research or university hospitals (61.9%) and actively evaluated pediatric patients. Notably, 57.0% reported examining ≥ 200 pediatric patients per month, with pediatric specialists and subspecialists bearing the highest clinical workload. Detailed demographic and professional characteristics are summarized in Table 1.

IEI Education, Clinical Exposure, and Diagnostic Experience

IEI-related education varied significantly across specialties ($p < 0.001$). Pediatric specialists and subspecialty trainees were the groups most likely to have received IEI training during both medical school and residency (up to 60%–65%), whereas family medicine and general practitioners predominantly received such education only during medical school.

Clinical exposure to IEI-related presentations also differed markedly. Recurrent infections were frequently encountered across all groups but were significantly more common among pediatric clinicians (94–100%) compared with family physicians and general practitioners (80–82%, $p < 0.001$). Similarly, frequent antibiotic use in children was observed almost universally in pediatric groups (98–100%) but at lower rates in primary care (82–92%).

Table 2. Comparison of IEI-related education, clinical exposure, and diagnostic practices across specialties (N = 488).

Variable	FMR n (%)	FMS n (%)	PR n (%)	PS n (%)	PSR n (%)	PSS n (%)	GP n (%)	p-value
IEI education received								
Not sure	4 (7.8)	2 (3.2)	4 (4.3)	0 (0.0)	1 (2.7)	0 (0.0)	5 (6.7)	
Yes: Medical school	37 (72.5)	41 (65.1)	30 (31.9)	14 (12.3)	5 (13.5)	14 (25.9)	69 (92.0)	
Yes: Residency	4 (7.8)	3 (4.8)	13 (13.8)	38 (33.3)	7 (18.9)	11 (20.4)	0 (0.0)	<0.001
Both periods	4 (7.8)	15 (23.8)	45 (47.9)	58 (50.9)	24 (64.9)	29 (53.7)	1 (1.3)	
No	2 (3.9)	2 (3.2)	2 (2.1)	4 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Recurrent infections								
Yes	42 (82.4)	50 (79.4)	94 (100)	112 (98.2)	31 (83.8)	4 (88.9)	60 (80.0)	<0.001
No	9 (17.6)	13 (20.6)	0 (0.0)	2 (1.8)	6 (16.2)	6 (11.1)	15 (20.0)	
Encountering frequent antibiotic use								
Yes	48 (94.1)	60 (95.2)	92 (97.9)	114 (100)	37 (100)	54 (100)	72 (96.0)	<0.001
Awareness: “Frequent antibiotic use $\rightarrow$ Possible IEI								
Yes	48 (94.1)	60 (95.2)	92 (97.9)	114 (100)	37 (100)	54 (100)	72 (96.0)	0.051



Variable	FMR n (%)	FMS n (%)	PR n (%)	PS n (%)	PSR n (%)	PSS n (%)	GP n (%)	p-value
Evaluated an IEI-diagnosed patient								
Yes	13 (25.5)	20 (31.7)	65 (69.1)	106 (93.0)	33 (89.2)	48 (88.9)	25 (33.3)	<0.001
Approach when suspecting IEI								
Did not suspect/No	26 (51.0)	30 (47.6)	23 (24.5)	7 (6.1)	1 (2.7)	3 (5.6)	41 (54.7)	<0.001
Suspected-Referred	22 (43.1)	31 (49.2)	52 (55.3)	53 (46.5)	17 (45.9)	20 (37.0)	30 (40.0)	
Suspected-Diagnosed self	3 (5.9)	2 (3.2)	19 (20.2)	54 (47.4)	19 (51.4)	31 (57.4)	4 (5.3)	
Need for institutional IEI awareness meetings								
Yes	38 (74.5)	46 (73.0)	87 (92.6)	92 (80.7)	35 (94.6)	46 (85.2)	56 (74.7)	<0.001
No	6 (11.8)	5 (7.9)	4 (4.3)	16 (14.0)	1 (2.7)	5 (9.3)	4 (5.3)	
Not sure	7 (13.7)	12 (19.0)	3 (3.2)	6 (5.3)	1 (2.7)	3 (5.6)	15 (20.0)	

FMR: Family Medicine Resident; FMS: Family Medicine Specialist; PR: Pediatrics Resident; PS: Pediatrics Specialist; PSR: Other Pediatric Subspecialty Resident; PSS: Other Pediatric Subspecialty Specialist; GP: General Practitioner; IEI: Inborn Errors of Immunity; IMF: Jeffrey Modell Foundation; an international advocacy organization that developed the “10 Warning Signs” to promote early recognition of primary immunodeficiency disorders.

Overall, 63.5% of participants had previously evaluated a child diagnosed with IEI, but this proportion ranged from 88%–93% among pediatric specialists to only 25%–33% in family medicine and general practice ($p<0.001$). The ability to establish an IEI diagnosis also showed wide variation: pediatric subspecialists (57.4%) and pediatricians (47.4%) reported the highest rates, whereas family physicians and general practitioners rarely made the diagnosis themselves (3–6%). Full comparative results are presented in Table 2.

Recognition of IEI-Associated Clinical Features

Recognition of IEI-associated clinical warning signs demonstrated substantial variability across specialties, with clear gradients favoring pediatric clinicians. As illustrated in Figure 1a, pediatric subspecialists consistently exhibited the highest recognition across all five major clinical domains infectious, autoimmune/inflammatory, growth/genetic, neurological/syndromic, and dermatologic/mucocutaneous while family medicine physicians and general practitioners showed significantly lower awareness patterns ($p<0.001$ across domains).

Infectious manifestations were the best-recognized category overall; however, major intergroup differences remained. Pediatric specialists identified high-risk infections, such as recurrent meningitis and recurrent sepsis, with near-universal recognition (94–98%), and recognition of ≥ 2 pneumonias per year, chronic diarrhea, or persistent viral infections frequently exceeded 90%. Pediatric residents and subspecialty trainees also demonstrated similarly high levels of awareness (85%–92%). In contrast, family medicine physicians and general practitioners showed substantially lower recognition, often ranging between 55% and 72% depending on the specific indicator, particularly for deep-seated infections and chronic viral illnesses. All infectious subdomains differed significantly between pediatric and non-pediatric clinicians ($p<0.001$) (Figure 1b).

Awareness of autoimmune and inflammatory features revealed even more pronounced differences. Pediatric subspecialists demonstrated strong recognition of autoimmune cytopenias and granulomatous inflammation, with rates ranging from 63%–78%, whereas pediatric specialists exhibited slightly lower but still high awareness. Recognition among family medicine physicians and general practitioners, however, was markedly reduced, often ranging only between 20% and 40%, with granulomatous inflammation and IBD-like enteropathy being among the least recognized features. These differences were again highly significant across all subdomains ($p<0.001$) (Figure 1c).

Dermatologic and mucocutaneous manifestations were recognized at moderate-to-high levels overall, but again with substantial specialty-based variation. Pediatric specialists identified persistent oral candidiasis, severe eczema, recurrent skin abscesses, and extensive fungal infections with very high recognition (90–95%), and pediatric residents demonstrated similarly strong awareness (78–90%). Family medicine physicians and general practitioners had significantly lower recognition across nearly all mucocutaneous indicators, most often ranging from 50%–57%. Specialty differences in this domain were also significant across all subcomponents ($p<0.001$) (Figure 1d).

Neurological and syndromic indicators also revealed sharp intergroup discrepancies. Pediatric subspecialists recognized developmental delay, microcephaly, ataxia, pigmentary abnormalities, and oculocutaneous albinism at rates between 70% and 82%, whereas pediatric specialists maintained moderately high recognition of 60%–75%. In stark contrast, family medicine physicians and general practitioners showed considerably lower awareness, frequently between 13% and 30% depending on the specific feature. All comparisons across specialties were statistically significant ($p<0.001$) (Figure 1e).



Growth, genetic, and structural features showed the widest specialty-based disparities among all domains. Pediatric clinicians recognized failure to thrive, consanguinity, early sibling death, and dysmorphic features with rates typically between 88% and 95%, and many structural anomalies (e.g., congenital cardiac or skeletal defects) were correctly linked to IEI in 70%–85% of pediatric respondents. In comparison, recognition among family medicine physicians remained substantially lower 52–57% for failure to thrive and generally below 50% for genetic red flags, such as consanguinity or

early sibling death. General practitioners demonstrated the lowest recognition in this domain, often between 35% and 48%. These findings were uniformly significant ($p < 0.001$) (Figure 1f).

Across all 26 clinical subdomains within the five major categories, pediatric subspecialists consistently demonstrated the highest recognition, followed by pediatric specialists and pediatric residents. Family medicine physicians exhibited moderate awareness, whereas general practitioners had the lowest recognition patterns.

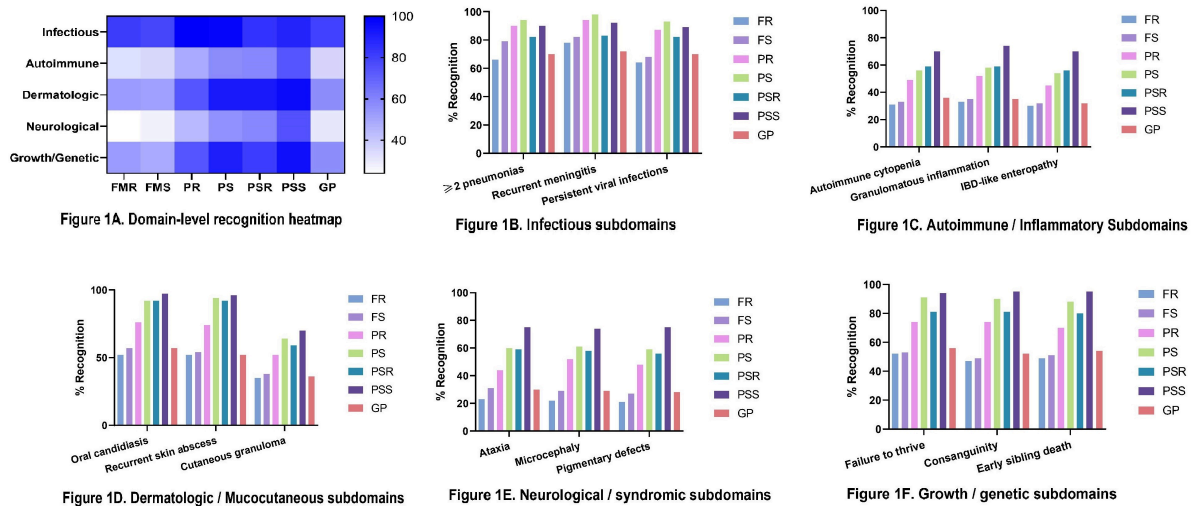


Figure 1. Recognition of IEI-related clinical features across specialties. (A) Domain-level heatmap of overall recognition across five major IEI-related clinical domains. (B) Recognition of infectious subdomains (≥ 2 pneumonias/year, recurrent meningitis, and persistent viral infections). (C) Autoimmune/inflammatory subdomains (autoimmune cytopenia, granulomatous inflammation, and IBD-like enteropathy). (D) Dermatologic/mucocutaneous subdomains (oral candidiasis, recurrent skin abscesses, and cutaneous granulomas). (E) Neurological/syndromic subdomains (ataxia, microcephaly, and pigmentary defects). (F) Growth/genetic subdomains (failure to thrive, consanguinity, early sibling death).

FMR: Family Medicine Resident; FMS: Family Medicine Specialist; PR: Pediatrics Resident; PS: Pediatrics Specialist; PSR: Other Pediatric Subspecialty Resident; PSS: Other Pediatric Subspecialty Specialist; GP: General Practitioner; IBD: Inflammatory bowel diseases.

Diagnostic Approach and Laboratory Use

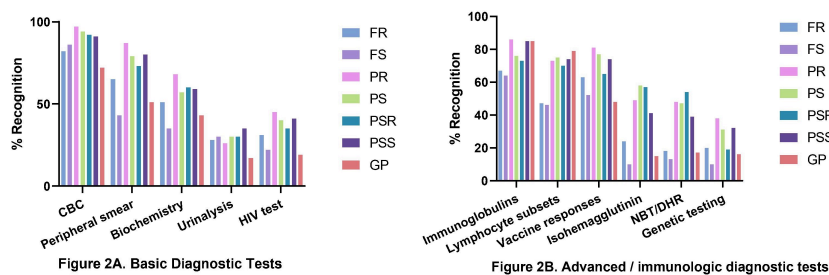


Figure 2. Diagnostic test use across specialties for suspected Inborn Errors of Immunity. (A) Use of basic laboratory tests, including complete blood count (CBC), peripheral smear, biochemistry, urinalysis, and HIV testing. (B) Use of immunologic and advanced tests, including serum immunoglobulins, lymphocyte subsets, vaccine response assessment, isohemagglutinin titers, neutrophil function tests (NBT/DHR), and genetic testing. Pediatric specialties demonstrated significantly higher use of advanced diagnostic modalities.

FMR: family medicine resident; FMS: family medicine specialist; PR: pediatrics resident; PS: pediatrics specialist; PSR: other pediatric subspecialty resident; PSS: other pediatric subspecialty specialist; GP: general practitioner; HIV: human immunodeficiency virus

Table 3. Laboratory investigations requested for suspected Inborn Errors of Immunity (IEI), stratified by specialty (N = 488).

Test	FMR n (%)	FMS n (%)	PR n (%)	PS n (%)	PRS n (%)	PSS n (%)	GP n (%)	p-value
Complete blood count	42 (82.4)	54 (85.7)	91 (96.8)	107 (93.9)	34 (91.9)	49 (90.7)	54 (72.0)	<0.001
Peripheral smear	33 (64.7)	27 (42.9)	82(87.2)	90 (78.9)	27 (73.0)	43 (79.6)	38 (50.7)	<0.001
Biochemistry panel	26 (51.0)	22 (34.9)	64 (68.1)	65 (57.0)	22 (59.5)	32 (59.3)	32 (42.7)	<0.001
Urinalysis	14 (27.5)	19 (30.2)	24 (25.5)	34 (29.8)	11 (29.7)	19 (35.2)	13 (17.3)	0.072
Lymphocyte subset analysis	24 (47.1)	29 (46.0)	69 (73.4)	86 (75.4)	26 (70.3)	40 (74.1)	59 (78.7)	<0.001
Serum immunoglobulins (IgG, IgA, IgM, and IgE)	34 (66.7)	40 (63.5)	81 (86.2)	87 (76.3)	27 (73.0)	46 (85.2)	64 (85.3)	<0.001
Vaccine response	32 (62.7)	33 (52.4)	76 (80.9)	88 (77.2)	24 (64.9)	40 (74.1)	36 (48.0)	<0.001
Isohemagglutinin titers	12 (23.5)	6 (9.5)	46 (48.9)	66 (57.9)	21 (56.8)	22 (40.7)	11 (14.7)	<0.001
HIV test	16 (31.4)	14 (22.2)	42 (44.7)	46 (40.4)	13 (35.1)	22 (40.7)	14 (18.7)	0.003
NBT/DHR test (neutrophil function)	9 (17.6)	8 (12.7)	45 (47.9)	54 (47.4)	20 (54.1)	21 (38.9)	13 (17.3)	<0.001
Genetic test (panel / NGS)	10 (19.6)	6 (9.5)	36 (38.3)	35 (30.7)	7 (18.9)	17 (31.5)	12 (16.0)	<0.001
No test ordered → direct referral to the higher center	43 (84.3)	54 (85.7)	93 (98.9)	108 (94.7)	34 (91.9)	50 (92.6)	55 (73.3)	<0.001

FMR: Family Medicine Resident; FMS: Family Medicine Specialist; PR: Pediatrics Resident; PS: Pediatrics Specialist; PRS: Other Pediatric Subspecialty Resident; PSS:Other Pediatric Subspecialty Specialist; GP :General Practitioner; NGS: Next-Generation Sequencing; NBT/DHR : Nitroblue Tetrazolium Dihydrorhodamine Test; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgE: Immunoglobulin E; HIV: Human Immunodeficiency Virus.

Basic and advanced immunologic tests differed significantly across specialties ($p<0.001$). As summarized in Table 3, pediatric clinicians particularly pediatric subspecialists utilized CBC, immunoglobulins, lymphocyte subsets, vaccine antibody titers, oxidative burst assays, and genetic testing substantially more often than family medicine physicians and general practitioners. Figure 2 visualizes these specialty-based patterns.

Referral Patterns

Most physicians indicated a preference for referring suspected IEI cases to higher-level or specialized centers. Overall referral frequency was high (89.5%), and pediatric clinicians demonstrated the highest referral tendency, with rates consistently exceeding 90%. Although general practitioners reported the lowest referral rate among all groups (73.3%), referral remained the predominant approach even within this specialty. These specialty-based differences in referral behavior are summarized in Table 3.

Ranges

Accuracy in identifying age-specific lymphocyte reference ranges varied across specialties. Correct responses ranged from 50%–76% among pediatric specialists and subspecialists, 14–45% among family medicine physicians, and 18–37% among general practitioners ($p < 0.001$). Overall, 78.5% of participants indicated that persistent lymphopenia should prompt further evaluation for a possible IEI. Awareness of Jeffrey Modell Warning Signs and Training Needs.

Awareness of the Jeffrey Modell Foundation 10 warning signs demonstrated substantial specialty-based differences. Overall, only 52.7% of participants had previously heard of the JMF warning signs, but recognition varied markedly between groups: awareness was significantly higher among pediatric specialists (63%–82%) compared with family medicine physicians (20–33%) and general practitioners (25%) ($p<0.001$).

After being presented with the warning signs during the survey, 44.3% of physicians indicated that some of their current patients would require further evaluation for a possible IEI, with the highest proportion reported among family medicine physicians (65%).

Willingness to pursue additional IEI-focused education was high across all specialties: 82% of participants indicated a desire to receive further training, with enthusiasm exceeding 90% among pediatric clinicians. Knowledge and awareness metrics including familiarity with the JMF warning signs and recognition of age-specific lymphocyte reference values are summarized in Table 4.



Table 4. Knowledge of IEI warning signs, age-specific lymphocyte reference values, and educational needs across specialties (N = 488).

Variable	FMR n (%)	FMS n (%)	PR n (%)	PS n (%)	PSR n (%)	PSS n (%)	GP n (%)	p-value
Heard of the JMF 10 warning signs?								
Yes	17 (33.3)	14 (22.2)	39 (41.5)	52 (45.6)	27 (73.0)	46 (85.2)	19 (25.3)	<0.001
No/ Not survive	34 (66.7)	49 (77.8)	55 (58.5)	62 (54.4)	10 (27.0)	8 (14.8)	56 (74.7)	
Correct lymphocyte cutoff (<1 year)	13(25.5)	9 (14.3)	42 (44.7)	52 (45.6)	18 (48.6)	34 (63.0)	14 (18.7)	<0.001
Correct lymphocyte cutoff (>1 year)	23 (45.1)	19 (30.2)	58 (61.7)	65 (57.0)	22 (59.5)	41 (75.9)	28 (37.3)	<0.001
After reviewing JMF signs, believes some patients should be evaluated for I.								
Yes	31 (60.8)	41 (65.1)	38 (40.4)	33 (28.9)	15 (40.5)	21 (38.9)	41 (54.7)	0.002
No/ Not survive	20 (39.2)	22 (34.9)	56 (59.6)	81 (71.1)	22 (59.5)	33 (61.1)	34 (45.3)	
Willing to receive further IEI training								
Yes	38(74.5)	43 (68.3)	80 (85.1)	93 (81.6)	32 (86.5)	49 (90.7)	52 (69.3)	<0.001
No/ Not survive	13 (25.5)	20 (31.7)	14 (14.9)	21 (18.4)	5 (13.5)	5 (9.3)	23 (30.7)	

FMR: family medicine resident; FMS: family medicine specialist; PR: pediatrics resident; PS: pediatrics specialist; PSR: other pediatric subspecialty resident; PSS: other pediatric subspecialty specialist; GP: general practitioner; IEI: inborn errors of immunity.

Barriers to IEI Diagnosis and Management

Participants identified several significant challenges that impede timely recognition and diagnosis of IEI. The most frequently reported barriers included limited laboratory capacity (58.3%), insufficient clinical training (54.2%), difficulty accessing immunology specialists (51.2%), complex or inefficient referral pathways (40.6%), delayed availability of laboratory results (37.7%), and issues related to patient non-adherence (34%).

These barriers were significantly more prominent among family physicians and general practitioners than pediatric clinicians ($p<0.001$). An overview of the most commonly reported obstacles is shown in Figure 3, and the survey items corresponding to these barrier domains are listed in Table 4 of the submitted tables document.

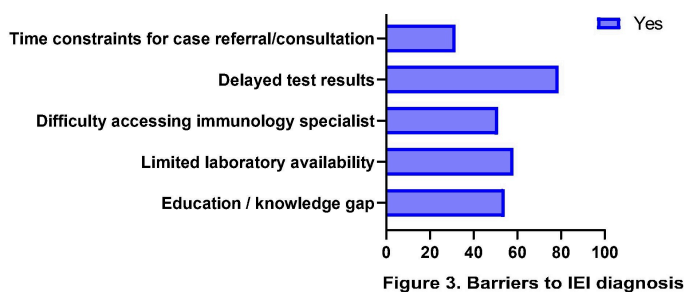


Figure 3. Reported barriers to the diagnosis of inborn errors of immunity. The most frequently reported challenges included limited laboratory availability (58.3%), lack of adequate education or knowledge (54.2%), difficulty accessing an immunology specialist (51.2%), and delayed test results (78.9%). Time constraints during consultations were also noted by 31.7% of participants.

DISCUSSION

IEI remain under-recognized worldwide despite substantial advances in diagnostic technologies and updated clinical definitions by the International Union of Immunological Societies (1,4,5). Recent systematic reviews and global analyses continue to highlight persistent gaps in awareness and delayed recognition across different healthcare settings (6-8). Delayed diagnosis carries significant consequences, including recurrent or severe infections, autoimmunity, end-organ damage, and avoidable morbidity (6-10). In this context, physician knowledge and early clinical suspicion constitute the cornerstone of timely IEI recognition. Our national, multi-specialty dataset of 488 physicians provides one of the most comprehensive assessments to date on IEI awareness, clinical reasoning, and diagnostic practices among frontline pediatric and primary care clinicians.

Comparison with International Literature

Consistent with studies from Ukraine, Brazil, Iran, and Peru, we found major variability in IEI-related knowledge across medical specialties. In the Ukrainian survey by Boyarchuk et al., pediatricians had the highest percentage of correct answers (76.9%), whereas non-pediatric specialties performed substantially lower (11). Similarly, the large Brazilian survey of 4026 physicians demonstrated that 77% of clinicians were unfamiliar with the Jeffrey Modell Foundation warning signs, and only 18% could correctly identify at least two-thirds of IEI-related clinical scenarios (12). Our findings parallel these results: pediatric specialists and pediatric subspecialists consistently outperformed family physicians

and general practitioners across all clinical domains infectious, autoimmune/inflammatory, dermatologic, syndromic, and growth/genetic.

Importantly, the magnitude of the knowledge gap in our cohort appears even more pronounced in growth/genetic and neurological/syndromic domains a pattern also observed in Peru and Brazil, where signs such as consanguinity, ataxia, pigmentary defects, or chronic diarrhea were under-recognized by more than half of respondents (11,12). These consistencies highlight the persistent challenge of identifying non-infectious presentations of IEI, despite growing global awareness that autoimmunity, lymphoproliferation, and immune dysregulation can dominate the phenotype in many monogenic diseases. Recent studies from Asia and Europe have similarly demonstrated substantial gaps in physician awareness, particularly regarding non-infectious and syndromic presentations of IEI in primary care settings (6-8).

Red Flags and Diagnostic Reasoning

Across all specialties, classic infectious red flags such as recurrent pneumonias or meningitis were recognized more reliably than autoimmune, mucocutaneous, or syndromic clues. This mirrors the observation by Dantas et al. that clinical situations involving atypical or opportunistic infections achieved the highest recognition scores, whereas features suggestive of syndromic IEIs (e.g., microcephaly, delayed separation of the umbilical cord, and dysmorphic facies) were identified by less than one-third of their nationwide sample (11,12).

Our findings confirm that infectious clues remain physicians' primary gateway to suspecting IEI, whereas non-infectious phenotypes which are increasingly prevalent in modern classifications remain largely unrecognized. This underscores the need for updating training materials that traditionally emphasize infection-dominant presentations (2).

Recognition of early-life warning signs, such as failure to thrive, parental consanguinity, and a history of early sibling death, remains particularly limited among frontline physicians in our cohort. These findings are particularly concerning given that such features often represent the earliest clinical indicators of inborn errors of immunity, particularly in populations with high consanguinity rates. Failure to identify these early clues may contribute to delayed diagnosis and prolonged diagnostic trajectories, which in turn may increase the risk of disease-related complications. Improving awareness of these growth- and genetic-related warning signs at the primary care level may therefore play a key role in facilitating earlier recognition and referral (9,13).

Clinical Exposure and Diagnostic Practices

We observed clear gradients in diagnostic engagement: pediatric subspecialists had the highest rates of evaluating IEI cases and independently making diagnoses, whereas family physicians and general practitioners almost universally relied on referral (7). This aligns with previous data suggesting that physicians outside tertiary centers often face structural barriers including limited access to immunologic tests, scarcity of immunology specialists, and insufficient institutional training (12). Similar patterns have been reported in recent physician surveys, where diagnostic suspicion and use of immunologic testing significantly increased following detailed patient history assessment and recognition of family history (6-8).

Laboratory utilization patterns in our study also reinforce this gap. While pediatric specialists reported high use of both basic (CBC, Ig levels) and advanced tests (lymphocyte subsets, vaccine responses, and DHR/NBT), their use was markedly lower among family medicine and general practice physicians. Comparable disparities have been reported in Brazil and Iran, where fewer than 20% of primary care physicians use immunologic investigations during diagnostic evaluation (12,14).

Role of IEI Education and Training

Our study highlights the cumulative impact of IEI-focused education. Physicians who received IEI training either in medical school or residency demonstrated significantly higher domain-level awareness and greater willingness to order appropriate diagnostic tests. This aligns with multivariate analyses from Brazil, where IEI education, familiarity with warning signs, and prior experience with recurrent infection patients were among the strongest independent predictors of higher knowledge scores (11,12).

Notably, only half of our cohort had ever heard of the JMF 10 warning signs, a finding consistent with both Brazilian (77% unaware) and Ukrainian (under-recognition of adult warning signs) data (12).

Despite these gaps, more than 80% of our participants expressed strong interest in receiving additional IEI training suggesting that structured educational interventions, including institutional awareness programs and national CME initiatives, are likely to be highly impactful.

Barriers to Diagnosis

Participants identified several systemic challenges that closely mirror barriers previously documented in Turkey, Peru, and Brazil (2,11,12). In our cohort, limited laboratory capacity, delays in test processing, difficulty accessing immunology specialists, and complex referral pathways emerged as major obstacles. Similar findings



were reported in the Turkish physician awareness study, wherein inadequate access to advanced immunologic testing and insufficient institutional support were highlighted as key contributors to diagnostic delay (2).

The Peruvian multicenter survey likewise demonstrated substantial infrastructural limitations, including restricted availability of specialized tests and geographic inequality in access to immunology services, which significantly hindered early IEI recognition. In Brazil, a nationwide survey of more than 4000 physicians revealed parallel constraints most notably lack of training, limited diagnostic resources in primary care settings, and the need for standardized referral pathways which were strongly associated with delayed or missed IEI diagnoses (12).

Together with our findings, these data suggest that diagnostic barriers are not isolated to any single healthcare system but represent a shared pattern across middle-income countries, where variability in resource distribution, specialist availability, and clinician training critically influences the timeliness and accuracy of IEI evaluation. Recent global analyses further support that such barriers persist across diverse healthcare systems, reinforcing the need for standardized diagnostic pathways and improved access to immunological evaluation (6-8).

Implications for Clinical Practice and Health Policy

Given Turkey's high rate of consanguinity and the expanding phenotype of monogenic immune dysregulation, the need for robust IEI awareness is particularly urgent. Integrating IEI modules into family medicine training, embedding early suspicion algorithms into

primary care workflows, enhancing laboratory capacity, and promoting the updated ESID/IUIS diagnostic criteria could substantially improve early detection (5,15).

Furthermore, our findings support the implementation of institutional IEI awareness meetings endorsed by more than 80% of respondents which could serve as critical platforms for multidisciplinary learning, case discussions, and dissemination of national referral pathways.

Strengths and Limitations

The strengths of this study include its large sample size, multi-specialty representation, domain-specific analysis of clinical awareness, and integration of laboratory and diagnostic behaviors. Limitations include self-reported data, potential sampling bias toward hospital-based physicians, and cross-sectional design, which precludes the evaluation of longitudinal knowledge change.

CONCLUSION

Our study reveals substantial variability and critical gaps in IEI knowledge across physician specialties in Turkey particularly in non-infectious domains and among primary care physicians. These findings align with global data and highlight the urgent need for structured, comprehensive IEI education and improved access to diagnostic resources. Enhancing awareness across all clinician groups is essential for reducing diagnostic delay, optimizing patient outcomes, and aligning with international standards for early detection of IEI.



Ethics Committee Approval Ethical approval for the study was obtained from the from the Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (Approval No: 3052 Date: 17/06/2025).

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