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Review Article

Health-related quality of life in primary immunodeficiencies: Impact of delayed diagnosis and treatment burden

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ABSTRACT

Accurate and timely diagnosis of primary immunodeficiencies (PID) is an ongoing effort. Individuals with PID can be severely impacted by their disease and many experience chronic complications, treatment burden, and reduced quality of life (QoL). This review focuses on the impact of delayed diagnosis and treatment burden on patient QoL and outcomes. Adults tend to experience longer delays in diagnosis than pediatric populations. The median diagnostic delay has reduced over recent decades, but remains high for some antibody deficiency variants, such as common variable immunodeficiency. The largest burden impacting QoL tends to be poorly controlled disease and persistent chronic conditions rather than treatment burden. Hospitalization, physician/emergency room visits, and bronchiectasis were the most expensive PID complications prior to diagnosis and cost analyses estimate cost reductions once appropriate treatment is initiated. A combination of poor awareness, lack of infrastructure, and resources supporting national registries play a major role in delayed diagnosis.

1. Introduction

Primary immunodeficiencies (PIDs) are a heterogenous group of disorders with over 400 different genetic mutations and associated morbidities included to date [1]. This number continues to grow as new mutations are identified and next generation sequencing (NGS) improves identification rates [1,2]. Individuals living with PID can be severely impacted by their condition. PIDs are genetic defects of the immune system that tend to predispose individuals to a range of serious infections, which are often chronic, recurring, and potentially incapacitating. Primary antibody deficiencies (sometimes also referred to as predominantly antibody deficiencies) are the most common type of PID and are characterized by an inability to produce clinically effective levels of immunoglobulin (Ig) [3]. Most primary antibody deficiencies characterized at the molecular level arise from defects linked to B-cell development and function [4]. Some of the most recognized antibody defects are common variable immune deficiency (CVID), X-linked agammaglobulinemia (XLA), severe combined immunodeficiency (SCID), immunoglobulin A (IgA) deficiency, specific antibody deficiency (SAD), and transient hypogammaglobulinemia of infancy [1,4]. Symptoms, severity, and typical onset varies between PIDs and, in addition to an increased infection frequency, can include autoimmunity and malignancy complications. Some individuals may be asymptomatic or a healthy carrier of a PID mutation. For example, IgA deficiency is the

Abbreviations: CBC, complete blood count; CG, calculated globulin; Coronavirus disease 2019, COVID-19; CVID, common variable immunodeficiency; ESID, European Society for Immunodeficiencies; HCP, healthcare professional; HRQoL, health-related quality of life; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; JMF, Jeffrey Modell Foundation; KREC, Kappa-deleting recombination excision circle; LFT, liver function test; IgRT, immunoglobulin replacement therapy; IVIG, intravenous immunoglobulin; NGS, next generation sequencing; PID, primary immunodeficiency; QoL, quality of life; SAD, specific antibody deficiency; SCID, severe combined immunodeficiency; SCIG, subcutaneous immunoglobulin; SID, secondary immunodeficiency; TREC, T cell receptor excision circle; UK, United Kingdom; US, United States; XLA, X-linked agammaglobulinemia.

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most common PID, with a prevalence up to 1 in 300 individuals, but it can be asymptomatic in approximately two thirds of cases [5,6]. Despite advances in PID awareness and diagnosis, it has been estimated that up to 90% of individuals living with PID remain undiagnosed [7]. If left undiagnosed or untreated, PIDs can lead to life-threatening infections [3].

True PID prevalence estimates are hindered by underdiagnosis, underreporting, and potentially death before diagnosis, especially in some infant cases [7,8]. Underdiagnosis can arise due to poor awareness, inadequate newborn screening, lack of family history or carrier testing, and asymptomatic PIDs [3,7,9]. Concerning issues faced by patients with PID are delays in diagnosis and misdiagnosis, both of which lead to a delayed initiation of appropriate treatment. Diagnostic delay, or delayed diagnosis, are defined as the elapsing time between the onset of PID symptoms and diagnosis (although exact definitions can vary between reports). The terms 'diagnostic delay' and 'delayed diagnosis' are both used in the literature and are used interchangeably in this review. Signs of reduction of in diagnostic delay has been observed in longitudinal studies. For example, a US epidemiology study conducted between 1976 and 2006 reported a decline in the median diagnostic delay from 17.5 years during 1976–1986 to 2.7 years in those diagnosed after 1996, but further improvement is needed [10]. The negative consequences of diagnostic delay can include multiple hospital admissions, preventable infections, end-organ damage such as bronchiectasis or hearing loss, and sometimes neurologic sequelae secondary to a central nervous system infection [11]. Where immunoglobulin replacement therapy (IgRT) is initiated, an additional concern can be the treatment-related burden, including the need to go to a hospital/infusion center for infusions, systemic adverse events, and cost of medication [12].

Treatments for PID can include IgRT, prophylactic antibiotic therapy, or immunosuppressants to improve symptom control in cases of associated autoimmune conditions, or hematopoietic stem cell transplantation or gene therapy to correct the abnormality in the genome [13]. Where appropriate, IgRT is typically offered for many PIDs as a first-line treatment to help reduce infection rates allowing patients to live relatively normal lives with fewer severe infections [12,13]. Opportunistic infections usually develop in the sinuses, ears, and lungs, but may be self-limiting or manageable without treatment. Not all patients require, or will receive IgRT, and in some cases close monitoring or prophylactic antibiotic therapy may be considered as the most appropriate treatment strategy [14].

Both delayed diagnosis and treatment burden can negatively impact the health-related quality of life (HRQoL) of patients with PID [4,11]. HRQoL is a particularly important factor in PID due to the complexity and often long-term nature of patient management and can impact treatment adherence [15]. The aim of this review is to compile the evidence on HRQoL in patients with PID with a focus on the impacts of diagnostic delay and IgRT treatment burden. The treatment burden presented by alternative treatments, such as prophylactic antibiotic, is also considered in this review.

2. Review methodology

A narrative review approach was chosen to summarize key evidence across a range of PIDs. To generate a comprehensive list of relevant publications for potential inclusion, PubMed and Cochrane databases were searched. In addition, internet searches were conducted to capture relevant articles missed from the database searches and additional articles were identified by the authors and from reference lists of articles identified from the database searches. Publications were limited to human studies and reviews, those written in the English language, and those published from January 1, 2010 to January 22, 2021. This cut-off date was selected in line with the year that the first subcutaneous immunoglobulin (SCIG) was approved for use in PID. Key search terms included: primary immunodeficiency, diagnostic delay, treatment burden and treatment satisfaction. See Supplementary Table 1 for the full list of search terms. Duplicates and irrelevant publications, such as those not in humans or those not reporting diagnostic delay or HRQoL, were excluded. The search aimed to identify all PID articles with content on HRQoL or quality of life (QoL), diagnostic delay, misdiagnosis, and/or treatment burden or treatment satisfaction (Supplementary Fig. 1).

3. Literature search – findings

We identified 380 articles from the original search. Of these, 274 were excluded due to lack of relevance after title screening, leaving 106 articles for full-text screening. Ten additional articles, not captured by the search but deemed of potential relevance, were added for full-text screening. Of 116 articles, 53 were excluded due to lack of relevance based on a full text screen. Finally, there were 63 articles (34 on delayed diagnosis or QoL linked to diagnostic timeliness and 29 on other relevant information such as economic burden, cost-analyses, genetic diagnosis, and general PID awareness) included for the current review (Supplementary Fig. 1).

3.1. Delayed diagnosis and misdiagnosis

Diagnostic delay has largely improved over time, but there remains some heterogeneity worldwide in the timeliness of an accurate PID diagnosis (Table 1 and Supplementary Fig. 2) [16]. Combining data from all PID national registries and epidemiology studies from the Jeffrey Modell Centers Network, one report extrapolated the data to the global population and estimated that only 10% of PIDs had been diagnosed worldwide, with adults experiencing more delays in diagnosis than pediatric populations [17]. A global dataset spanning 47 countries suggests that differences in prevalence may be partially a result of a country's economic status and the associated underdiagnosis or misdiagnosis; for example, countries that provide systematic newborn screening and PID registries often have a higher prevalence compared with 'developing' countries where infrastructure is limited and PID awareness is often lower [16,18]. The United Kingdom (UK) PID registry recognizes the degree of diagnostic delay as an important prognostic indicator, with longer delays negatively affecting outcomes [19]. In general, longitudinal studies are best placed to observe any trends in declining diagnostic delay across various PIDs by time period [10]. For example, diagnostic delay of primary hypogammaglobulinemia in a single center in the Czech Republic decreased from 5.5 years in the 1980s to 1 year by 2008 [20]. Episodes of pneumonia during the period prior to diagnosis also decreased to zero by 2008 [20]. A Brazilian study evaluated a pediatric cohort with hypogammaglobulinemia and found that pneumonia was the most common clinical manifestation before diagnosis. Episodes of pneumonia decreased with treatment initiated post-diagnosis, but pulmonary complications often persisted [21]. Moreover, patients with bronchiectasis were more likely to have had a longer diagnostic delay [21]. Gathman et al. compared diagnostic delay before and after 2000 in a CVID cohort from the European Society for Immunodeficencies (ESID) registry and found an overall decline in median diagnostic delay from 5 to 4.2 years, but this decline was only statistically significant for Spain (9 years to 4.6 years) [22]. In contrast, a 2019 German registry study investigated diagnostic delay by type of delay, either clinical or genetic delay, and found no significant decreases in clinical diagnostic delay over the last 50 years in various PIDs (including CVID, SCID, and agammaglobulnemia) [23]. An improvement in timeliness of genetic diagnosis was observed in SCID, where the average delay before 2006 was 2.43 years (median 1 year) compared with an average delay of 1 year (median 0 years) between 2007 and 2017 [23]. CVID had a median delay in clinical diagnosis of 3 years, but a median delay in genetic diagnosis of 9 years [23]. CVID is generally associated with the longest diagnostic delay for any PID, despite some registry data showing a decrease in delay over time [19,22,24–26]. The median delay in diagnosis for CVID is reported as 4–5 years in many European countries and delayed diagnosis is typically higher with early-

onset disease [22,25,27]. Onset often occurs at an early age, with 40% of males with CVID experiencing disease onset below 10 years old [22]. An analysis of Danish patients with CVID examined the 3 years prior to clinical diagnosis and demonstrated a higher utilization of healthcare resource compared with matched controls – the median number of consultations increased as the time to diagnosis decreased [28]. The study concluded that CVID should be a differential diagnosis among patients with multiple medical consultations in a short timeframe in combination with raised inflammation markers and requests for pulmonary function tests in patients younger than 40 years [28]. In a study of patients with primary antibody deficiency in Iran, there was an average delay of 4.8 years in diagnosis for XLA, despite the severity of symptoms associated with XLA [29]. The longest delays for XLA and CVID were reported in an Malaysian study at over 5 and nearly 14 years, respectively [26]. A 2018 Australian retrospective study in a range of PIDs reported a higher median diagnostic delay (7.5 years) than most European reports [11,30]. Patients with XLA experienced a significantly shorter median delay (1 year), but patients with CVID experienced longer delays (9 years).

The practice of genetic testing remains underutilized and was not uniformly used for the patients in this study; however, 23% had an identified genetic cause for their PID [30]. Patients who had an identified genetic contribution to their disease were associated with a shorter delay to clinical diagnosis [30]. The practice of genetic testing remains underutilized. Molecular diagnosis can improve diagnosis timeliness and accuracy and in turn improves patient outcomes [4,16]. A 2020 global review of national PID registries reported that 13.2% of patients received a genetic diagnosis, with the highest rates observed in Asia and the Middle East (25.9%) [16]. Updates from the Iranian registry report a marginal shift towards improving diagnostic delay in newly diagnosed patients and this may be partially the result of the integration of molecular tests [31,32]. The 2014 Iranian registry update reported 52.0% of new patients were diagnosed within 1 year; in comparison the 2018 update reported 66.9% of new patients diagnosed within 1 year and a decline in those diagnosed with a greater than 5-year delay [31,32]. A French registry study reported significant decreases in genetic diagnostic delay based on decade of birth (1970s to 2010s), although genetic diagnosis was still low for patients with CVID, hypogammaglobulinemia, and IgA deficiencies [33]. A customized genetic testing program in place in New Zealand was assessed for clinical utility; the dedicated service enabled rapid results, reduced risk of laboratory errors, identified atypical PIDs, and allowed clinical decisions to be made in real time [34]. In addition, it proved a cost-effective solution for a relatively isolated country with a small population [34]. In contrast, an Indian single center registry cited availability and affordability of genetic testing as the main barriers to accurate diagnosis, although genetic testing was performed in 25% of patients in the registry [35]. The authors suggested that developing countries should establish specific centers for genetic diagnosis as well as identifying a need for a government-supported national registry [35].

3.1.1. Impact of diagnostic delay on patient outcomes

Delay in diagnosis contributes to delayed administration of specific treatments, increased morbidity (recurrent infections such as pneumonia or sinusitis), poor HRQoL, and mortality [10,36,37]. A European CVID registry from 1996 to 2006 reported that 20% of patients with CVID were diagnosed 15 years after symptom onset [38]. Similarly, a 2008 survey of 20 UK centers found that although PID diagnostic delay had reduced compared with earlier years, diagnostic delay was still $\geq$7 years in 27% of patients [27]. Among patients with delayed diagnosis, 66% had infections, 30% had respiratory complications, and 43% had anxiety/stress and depression [27]. Using European registry data, a 1.7% increased mortality risk in patients with CVID was estimated for each additional year of diagnostic delay [22]. An Italian study found that lower IgA levels (<8.0 mg/dL) at CVID diagnosis correlated with reduced patient survival, particularly in conjunction with older age at diagnosis [39]. Prior to population newborn screening, a United States (US) survey study in SCID compared outcomes in infants screened at birth and those with no screening [40]. Those without a family history had a diagnostic delay of 3.5 months and required, on average, nearly an additional 7 weeks of hospitalization. Patients who were diagnosed early, or prenatally, due to positive family history had higher survival rates than unsuspected cases (85% versus 42%) [40]. Patients who survived had an earlier initiation of treatment (average 29 weeks of age) compared with those who died (average 57 weeks of age).

Patients with PID have significantly lower HRQoL when compared with a healthy population, and earlier diagnosis is a factor associated with improved QoL (Table 2) [11,41]. Studies have shown that QoL in children with primary antibody deficiencies is often worse than the QoL of children with other chronic conditions, such as diabetes mellitus or congestive heart failure [42,43]. In addition to the anxiety associated with a prolonged diagnostic journey, other complications can manifest and impact QoL, such as chronic respiratory diseases or chronic diarrhea [11]. Patients remain at risk of a variety of complications not linked to diagnostic delay, such as an increased risk of cancer [44,45]. However, diagnosis can increase awareness of the higher risk of cancer. An ESID registry study on disease burden found that diagnostic delay was associated with a higher risk of solid tumor formation [46]. The impact of diagnostic delay on HRQoL and the patient-physician relationship can be long lasting and extend beyond diagnosis. An Iranian study focused on QoL reported that patients with a delayed diagnosis had significantly lower HRQoL compared with patients with a timely diagnosis, even after they had been diagnosed and received treatment [47]. Similarly, a UK survey found that only 40% of patients with a delayed diagnosis reported improvements in anxiety/stress and depression after diagnosis and treatment initiation [27]. In addition, a US survey found that patients with a poor health perception prior to the initiation of IgRT tended to retain a poor health perception [48]. Rider et al. found associations between worsening QoL and increasing functional limitations and organ impairment in adults with CVID [49]. These studies highlight the detrimental impact and pervasiveness of the complications prior to diagnosis and treatment initiation.

3.1.2. Causes of diagnostic delay

Diagnostic delay is defined as the elapsing time between the onset of PID symptoms and diagnosis, although exact definitions can vary between reports. The extent of delay by region reflects the awareness of PID among physicians. However, the underlying causes of diagnostic delay can be varied, cumulative, and differ between countries. A combination of poor awareness, especially among non-specialist healthcare professionals (HCPs), and lack of infrastructure and resources to support registry data collection and screening programs play a major role in diagnostic delay [16,50]. PID can go undetected due to the range of non-infectious manifestations or a focus on treating complications and missing the underlying cause. HCPs should be aware of the warning signs of PID, but diagnosis will often require expert physicians and access to special centers [51,52]. Inconsistencies in diagnostic criteria or patients being too ill to be investigated (particularly in SCID) can also cause delay [40]. Multidisciplinary and collaborative action is required at national and international levels rather than isolated efforts to spread consistent PID guidance. Genetic testing can diagnose PIDs faster but requires more awareness, accessibility, and uptake. The Jeffrey Modell Foundation (JMF) conducts a number of global awareness campaigns and in 2019 launched a free global genetic sequencing pilot program in an effort to improve rates of molecular diagnosis of PID [53]. A survey of the program showed that as a result of genetic sequencing, the clinical diagnosis was updated for 45% of patients and 36–40% changed their disease management or treatment [50]. Potential solutions to improve diagnosis are wider use of the calculated globulin (CG) test (globulin + albumin = total protein, liver function test [LFT]), included as part of an LFT that determines the serum globulin concentration [54,55]. Low CG i.e., $\leq$18 g/L has a positive predictive value of 100% for

Table 1
Publications reporting diagnostic delay estimates identified by literature search; including two examples from prior to the search criteria for additional context [16,19–27,29–32,36,37,39,40,66,87–95].

Region/ country	Publications reporting diagnostic delay	Indication	Study design (sample size, n)	Median diagnostic delay in years (unless stated otherwise)
Global				
Global	Abolhassani et al., 2020 *Time period: Mixed - N/A*	Various PIDs	Review of 18 national PID registries ($n = 15,939$)	PID: 2.24 *Longest: Malaysia 3.78* *Shortest: Iran 1.0*
Asia				
Iran	Aghamohammadi et al., 2011 *Time period: 1982–2007*	Various PIDs *(pediatric cohort)*	Single center, retrospective chart review ($n = 48$) *Includes analysis stratified by year of diagnosis*	Primary antibody deficiency: 2.9 *(overall) Diagnosed pre-1997: 4.7* *Diagnosed post-1997: 2.1*
	Aghamohammadi et al., 2014 *Time period: 2008–2012*	Various PIDs	Iranian registry study 3rd update ($n = 731$*) *new patients added since 2013	PID: 1.0 *52.0% diagnosed < 1 year; 65.0% diagnosed <2 years; only 17.6% were diagnosed > 5 years (from symptom onset)*
	Abolhassani et al., 2018 *Time period: 2013–2018*	Various PIDs	Iranian registry study 4th update ($n = 1395$*) *new patients added since 2013	PID: 0.8 *66.9% diagnosed < 1 year; 75.2% diagnosed <2 years; only 10.9% were diagnosed > 5 years (from symptom onset)*
	Alizadeh et al., 2020 *Time period: 2008–2017*	XLA	Case series ($n = 5$)	XLA: 4.8 (mean)
Kuwait	Al-Herz et al., 2010 *Time period: not specified*	Various PIDs *(pediatric cohort)*	Kuwait registry study – pediatric analysis ($n = 98$)	PID: 1.76 (mean) Primary antibody deficiency: 2.31 (mean)
	Al-Herz et al., 2012 *Time period: 2004–2011*	Various PIDs	Kuwait registry study 2nd update ($n = 176$)	PID: 2.0 (mean)
	Al-Herz et al., 2019 *Time period: 2004–2018*	Various PIDs	Kuwait registry study 3rd update ($n = 314$)	PID: 2.25 (mean) Primary antibody deficiency: 2.5 (mean)
Malaysia	Noh et al., 2013 *Time period: 1987–2006*	Various PIDs	Multicenter, retrospective chart review ($n = 51$)	CVID: 13.67 (mean) SCID: 0.38 (mean) XLA: 5.27 (mean)
Africa				
Morocco	Bousfiha et al., 2014 *Time period: 1998–2012*	Various PIDs	Moroccan registry study ($n = 412$)	PID: 2.0
Tunisia	Mellouli et al., 2015 *Time period: 1988–2012*	Various PIDs *(pediatric cohort)*	Tunisian registry study ($n = 710$)	PID: 1.5
Europe				
Europe	Gathmann et al., 2014 *Time period: 2004–2012*	CVID	ESID registry review – CVID cohort ($n = 2212$) *Includes analysis stratified by year of diagnosis*	CVID: 4.2 *Germany: 4.8* *Spain 4.6* *UK/France: 4.5* *The Netherlands: 2.7* *Czech Republic 2.3* *Diagnosed pre-2000: 5.0* *Diagnosed post-2000: 4.2*
Czech Republic	Litzman et al., 2010 *Time period: 1981–2008*	Hypogammaglobulinemia	Single center, retrospective chart review ($n = 33$) *Includes analysis stratified by year of diagnosis*	*Hypogammaglobulinemia:1.0* *Diagnosed in 1980s: 5.5* *Diagnosed in 1990s: 3.5* *Diagnosed 2001–2008: 1.0*
France	CEREDIH group, 2010 *Time period: 2005–2009*	Various PIDs	France registry study	PID: 1.0 CVID: 6.0 SCID: 0.2 Hypogammaglobulinemia: 2.3
	Mahlaoui et al., 2019 *Time period: 2008–2018*	Various PID	French registry study looking at genetic diagnosis ($n = 3405$)	PID: 0.7 (*genetic delay) *NB *Genetic diagnostic delay has dramatically decreased when stratified by decade of birth (1978–2018)*
Germany	Gathmann et al., 2014 *Time period: 1987–2010*	Various PIDs	German registry study ($n = 1368$)	CVID: 4.0 Hypogam: 1.0
	El-Helou et al., 2019 *Time period: 2012–2017*	Various PIDs	German registry study update ($n = 2453$)	CVID: 3.0 IgA deficiency: 3.0 SCID: 0.43 *NB No difference observed in diagnostic delay when stratified by year diagnosed (1957–2017)*
Greece	Michos et al., 2014 *Time period: 1981–2010*	Various PIDs *(pediatric cohort)*	Single center, retrospective chart review ($n = 147$)	PID: 0.9 Primary antibody deficiency: 5.1 CVID: 5.2 XLA: 0.2
Italy	Graziano et al., 2017 *Time period: 1987–2017*	CVID	Multicenter, retrospective chart review ($n = 75$)	CVID: 7.0 *NB Low IgA levels at diagnosis (>8 mg/dL) was associated with worse outcomes/reduced survival (including higher age of diagnosis or symptom onset)*
Switzerland	Marschall et al., 2014 *Time period: 2008–2014*	Various PIDs	Multicenter, registry study ($n = 348$)	CVID: 5.95 Hypogammaglobulinemia: 3.17
UK		CVID	Multicenter, retrospective chart review ($n = 62$)	CVID: 4.0

(*continued on next page*)

Table 1 (*continued*)

Region/ country	Publications reporting diagnostic delay	Indication	Study design (sample size, n)	Median diagnostic delay in years (unless stated otherwise)
	Grigoriadou et al., 2010 [abstract only] *Time period: 2008*			
	Edgar et al., 2013 *Time period: 2008–2012*	Various PIDs	UK registry study ($n = 2229$) *Includes analysis stratified by age at diagnosis and gender*	CVID: 5.0 Agammaglobulinemia: 1.0 Other hypogammaglobulinemia: 1.0 *CVID diagnosed ≤ 16 years old: 2.0* *CVID diagnosed ≥ 30 years old: 8.0*
	Holding et al., 2015 *Time period: 2004–2007*	CVID	Single center, retrospective analysis ($n = 8$) *(with prospective routine practice element)*	CVID: 4.0
	Shillitoe et al., 2018 *Time period: 2012–2017*	Various PIDs	UK registry study update ($n =$ 3889, excl. SID patients)	CVID: 4.0 SCID: 0.17
North America				
Mexico	Guanı-Guerra et al., 2017 *Time period: not specified*	Various PIDs	Multicenter, retrospective chart review ($n = 44$)	PID: 2.17
USA	Chan et al., 2011 *Time period: 2009*	SCID *(pediatric cohort)*	Observational, survey study ($n =$ 138)	SCID: 0.29 (mean)
South America				
Brazil	Dorna et al., 2016 *Time period: 2005–2010*	hypogammaglobulinemia *(pediatric cohort)*	Single center, retrospective chart review ($n = 30$)	Hypogammaglobulinemia: 4.7
Peru	Veramendi-Espinoza et al., 2017 *Time period: 2013–2015*	Various PIDs *(pediatric cohort)*	Single center, retrospective chart review ($n = 45$)	PID: 1.0 Primary antibody deficiency: 1.17
Australia/Oceania				
Australia	Slade et al., 2018 *Time period: 2001–2017*	Various PIDs	Multicenter, retrospective chart review ($n = 179$)	CVID: 9.0 XLA: 1.0

Diagnostic delay is defined as the time between first symptom onset and the age of clinical diagnosis – although exact definitions may vary between publications. *Genetic diagnostic delay was defined as the time interval between the date of clinical diagnosis of a PID and the date on which the genetic test results were available. CVID, common variable immunodeficiency; PID, primary immunodeficiency; SCID, severe combined immunodeficiency; UK, United Kingdom; US, United States; XLA, X-linked agammaglobulinemia.

hypogammaglobulinemia. Additionally, a complete blood count (CBC) and serologic tests of Ig levels should be consider for initial workup [56]. Ensuring availability and patient access to diagnostic facilities, expert physicians, screening, and genetic testing are current priorities when considering how to improve outcomes for patients with PID [7]. Accessibility to these diagnostic resources encompasses geographic accessibility, financial accessibility, and HCP/government acceptability and is largely driven by a country's economic status and population burden. The increasing use of telemedicine and regional referral networks are two examples being adapted to improve access to care in Asian PID communities.

3.1.3. Cost implications of delayed diagnosis

The cost implications for healthcare systems and patients as a result of diagnostic delay are difficult to assess due to regional differences and the variety of direct and indirect costs. Rapid and accurate diagnosis facilitates better use of healthcare resource in the long term and is associated with substantial cost savings due to the decreased avoidable complications [45]. JMF studies have attempted to estimate the annual associated costs of the most frequent conditions affecting patients with PID [45,50]. Most of the complications were those that can be significantly reduced with the appropriate disease management and treatment triggered by an accurate diagnosis, such as respiratory infections and bacterial pneumonia [50]. Hospitalization days, physician/emergency room visits, and bronchiectasis were the most expensive PID complications and expected to reduce once treatment is initiated [50]. A review of cost-effectiveness in PID concluded that early diagnosis reduced healthcare consumption and resulted in better outcomes for patients [57]. Comparisons of costs in CVID pre- and post-diagnosis have demonstrated cost savings ranging from $6500 to $108,463 (US) per patient per year and equate to patients with a diagnosis costing approximately 4.5 times less than patients without a diagnosis [57,58]. Another study estimated annual costs post-diagnosis in PID and found cost-savings even when factoring in regular IgRT [59].

Without timely diagnosis and treatment, SCID is often fatal and can accumulate large healthcare costs. The cost-effectiveness of population newborn screening for SCID has been demonstrated in several European and US studies [57,60–62]. However, a Dutch study estimated an overall cost increase with screening and recommended pilot screening in Europe to improve cost-effectiveness estimates [63]. Screening for SCID was initiated in the US in 2008 and is currently conducted in 45 states. The Centers for Disease Control and Prevention (CDC) is aiming to advance SCID screening nationwide [64]. Modell et al. estimated the cost of care for one infant with SCID, not diagnosed through newborn screening, could be more than the cost of screening for an entire state or regional population [65]. As of 2019, up to 20 other countries are implementing SCID newborn screening or pilot programs [62]. SCID can be detected by a T cell receptor excision circle (TREC) assay using the same dried blood spot samples already collected from newborns to screen for other genetic disorders. The TREC assay identifies low levels of naïve T cells and has a proven high specificity and sensitivity to accurately identify most infants affected with SCID. Kappa-deleting recombination excision circle (KREC) is an additional diagnostic test being developed, which may offer some advantages by identifying B cell defects that would be missed by a TREC assay. Newborn screening programs are starting to implement the use of both assays in conjunction [62]. Newborn screening should be complimented with medical education and CG testing (as outlined earlier). CG screening, with defined cut-off values, can aid detection of both primary and secondary antibody deficiencies and be a useful tool for reducing diagnostic delay and time to treatment [55,66]. CG is a novel and rapid method for estimating IgG levels that is widely available, although currently underutilized [55,66]. Research is ongoing as part of a CG project to evaluate the role and benefit of CG as a screening tool in pediatric populations. Moreover, CG

Table 2
Studies of patients with late diagnosis/diagnostic delay reporting HRQoL and/or treatment satisfaction between 2010 and 2020.

Publication	QoL tool(s) used	Outcomes
Hamid et al., 2018	• PedsQL	• Patients with SCID and delays in diagnosis or HSCT were reported to have a lower quality of life index • Approx. 85% of the patients with Artemis SCID had continued medical problems
Ataeninia et al., 2017 (Iran, $n = 70$)	• SF36 health survey • PedsQL	• Increased infections and hospitalizations were associated with poor QoL scores • Longer diagnostic delay was associated with worse physical component QoL scores ($p = 0.046$)
Rider et al., 2017 (US, $n = 945$)	• SF12 health survey (adults) • SF10 health survey (children)	• Higher QoL scores in CVID were associated with early diagnosis • Other factors associated with better QoL: younger age, male sex, less functional impairment, less/lack of organ-associated disease, no post-infusion fatigue, and IgRT in a home setting.
Aghamohammadi et al., 2011 (Iran, $n = 36$)	• SF36 health survey	• Patients with long delay diagnosis showed significantly lower SF36 scores ($p = 0.003$) • Patients with timely diagnosis and management had fewer complications • Patients with severe PID had low QoL even with diagnosis and appropriate management
Grigoriadou et al., 2010 (UK, n = 62)	• Case review study	• Patients with a late CVID diagnosis experienced infections (66%), respiratory complications (30%), and anxiety/stress and depression (43%)

CVID, common variable immunodeficiency; HRQoL, health-related quality of life; IgRT, immunoglobulin replacement therapy; PedsQL, pediatric quality of life; PID, primary immunodeficiency; QoL, quality of life; SF10/12/36, short form 10/12/36 questions.

screening may be of particular interest to adults due to the longer delays in diagnosis they tend to experience.

NGS can decrease time to diagnosis, improve diagnosis rates, allows for rapid and relatively inexpensive sequencing of DNA and RNA, and could transform the approach to diagnosis in PID if availability were improved [50,67]. Cost and insurance restrictions have been cited as barriers to genetic testing, with a survey of immunologists citing insurance denials for genetic testing as the most common denial received for clinical tests [68]. However, the cost of genetic testing should be considered negligible in comparison to the ongoing expenses associated with PID complications [59]. Details on the various genetic tests available for PID, including practical aspects, advantages, and limitations and challenges in low-resource environments have been well reviewed elsewhere and can help clinicians determine the best approach when ordering tests and aiming to establish genetic testing [69,70]. In addition to perceived cost barriers, competence, interpretation, and translation into clinical care are other obstacles to overcome in establishing NGS as part of normal clinical practice [71].

4. Treatment benefit and burden

IgRT can be administered as intravenous immunoglobulin (IVIG) or SCIG, and the degree of benefit perceived will vary between patients and their preferred mode of administration. The UK Primary Immunodeficiency registry reports the benefits of maintaining a higher Immunoglobulin G (IgG) trough level, which is associated with reduced infection rates and improved survival outcomes [72]. Patients receiving IgRT for their condition in the registry were primarily patients with CVID (50.1%), XLA (7.3%) and SAD (4.5%) [72]. Within the registry the median IgG trough levels provided by IVIG and SCIG were 9.9 g/L and 9.0 g/L, respectively [72]. A European study of CVID treatment practices found that patients with IgG trough levels ≥4 g/L had fewer serious bacterial infections than patients with trough levels <4 g/L [22]. However, this benefit did not translate into improved QoL, which may be due to the presence of moderate infections and non-infectious complications [22]. A survey of patients treated with SCIG, 75% of whom had a PID, reported prohibitive factors for treatment included technical issues and issues with ancillary supplies. However, high treatment satisfaction and increased well-being were reported when treatment was adjusted to fit into patients' everyday lives [73]. A pooled analysis of Phase III trials of SCIG found that switching from IVIG to SCIG improved patient self-reported health status and HRQoL. The biggest improvement was patient-reported convenience and less time off work or school versus IVIG [74]. Manual push SCIG offers an additional option for treatment individualization and is preferred over pump infusion by some patients, as it provides a quicker, simpler infusion and can reduce administration costs [75]. However, some patients may prefer the hands-free aspect of pump infusions. A 2018 systematic review assessed the perceived burden of IgG treatment from the patient perspective and concluded that overall patients with PID report a limited burden. However, there was a trend for preferring home-based treatment to further ease the burden [76]. IVIG and SCIG can both be administered in a home setting, although IVIG requires an HCP to conduct the infusion. From the perspective of caregivers of children with PID, a Polish study of parents/caregivers' treatment satisfaction found this was lower with SCIG compared with IVIG, which was attributed to the anxiety of administering infusions to their child, although it was accepted that IVIG placed a greater burden on missed school and work [77]. Patient preference for IVIG versus SCIG varies and although many patients prefer the convenience of SCIG, others prefer the reassurance of hospital-based treatment or HCP oversight during their infusions and the additional, regular HCP interaction this approach offers. Other studies of patients with PID found little difference in HRQoL between patients on IVIG and SCIG; the largest patient burden impacting QoL is poorly controlled disease and persistent chronic conditions, such as chronic lung disease and chronic diarrhea [49,78]. Regardless of administration route, patients with PID receiving longstanding IgRT generally report high satisfaction with their treatment, although their HRQoL is still lower compared with the normal population [79,80]. The same discrepancy between high treatment satisfaction with IgRT and suboptimal HRQoL was found in a global survey that identified several unmet needs in patients receiving IgRT, including an overall preference for a monthly treatment frequency, self-administration, home-administration, shorter administration duration, and fewer needle sticks [79]. A study assessing different IgRT infusion schedules in patients with CVID concluded that the impact on HRQoL was reduced when extensive patient education and therapy individualization was conducted beforehand [81]. An Iranian study found lower scores for the physical components of QoL was associated with increased infection episodes and hospitalizations in adult patients with PID. In contrast, younger patients with high hospitalizations had noticeably lower scores for social and emotional components, but unaffected QoL physical scores [41]. These findings suggest young patients may be more used to their physical limitations but also more impacted by fear of exposure to infectious agents [41]. A twelve-month observational study of upper airway infections in patients with primary antibody deficiency (the BIPAD study, CSL Behring, Switzerland) found that despite IgRT and the use of antibiotic prophylaxis, patients still experienced an increased frequency of viral infection and significant respiratory symptom burden compared with age-matched controls. In the context of the recent coronavirus disease 2019 (COVID-19) pandemic, this study highlights the need for effective infection control in this population [82]. A recent survey-based study

found that HRQoL had been impacted by the COVID-19 pandemic in patients with primary antibody deficiency due to an increased risk of anxiety and depression in particularly due to fears of running out of their medication or being at higher risk for COVID-19.

Many studies tend to utilize generic HRQoL tools when measuring QoL. A more sensitive approach to assess HRQoL and treatment satisfaction in patients with PID may be to use a disease-specific HRQoL tool that is designed to specifically probe the impact of complications and burdens that are relevant to patients with PID – factors that a generic tool may not be sensitive enough to capture [83]. Ballow et al. designed and validated a disease-specific HRQoL instrument to improve clinicians' understanding of patients with PID and help treatment optimization [84]. Disease-specific tools may allow for a clearer picture of the ongoing treatment (and disease) burden to patients and expose areas for adaption and improvement in patient management.

Previous retrospective studies have shown prophylactic antibiotics can be effective in preventing infections and some patients may benefit from prophylactic antibiotic without the need for IgRT [13,14]. A US study of patients with SAD compared IVIG or prophylactic antibiotics with clinical observation alone and found a statistically significant reduction in antibiotic prescriptions in treated patients compared with clinical observation [85]. Prophylactic antibiotic treatment requires optimization to determine the most appropriate antibiotic regimen for the patient; therefore, it is beneficial for the physician and patient to discuss a back-up plan [13]. A prospective, crossover trial comparing IgRT with prophylactic antibiotics in PID found similar efficacy over 2 years [14]. However, patients with persistent infections on prophylactic antibiotics had fewer infections when switched to IgRT [14]. Patients with PID with persistent infections despite antibiotic use should initiate IgRT and the derived benefit can be measured by the impact on infections before and after treatment initiation and through discussion with the patient. See Table 3 for a list of commonly reported burdens associated with PID management and suggested mitigation measures to combat these.

4.1. Balancing benefit and burden in PID treatment

Not all patients with PID will require IgRT, or therapy will be administered alongside prophylactic antibiotic use. Those with IgG <4 g/L are more likely to require IgRT, although patients with low IgG above 4 g/L can still benefit. However, the strategy of initiating IgRT based on low IgG levels alone is typically not adopted due to the expense of treatment and burden on patients if not required. Jolles et al. recommend that individuals with either low IgG or with a molecular diagnosis, but no other symptoms, should be monitored every 6–12 months and bacterial infections should trigger the use of antibiotics [13]. The increasing use of genetic testing in diagnosis should assist in targeting treatment benefit by defining patient profiles and individual risk factors leading to more individualized treatment strategies. Understanding the molecular basis of the PID allows selection of agents

Table 3
List of commonly reported burdens associated with PID management strategy.

Commonly reported burdens		Recommendations to ease burden or adjust treatment
No treatment – monitoring		
Higher risk of infection/patient anxiety		Patient education may ease anxieties over the infection risk, including discussing their care plan and options should treatment be needed. Alternatively, considering initiation of treatment may be required if the infection risk is high
Prophylactic antibiotic treatment		
Persistent infections		Consider a different antibiotic regimen or IgRT
Patient poor antibiotic tolerance		Consider a different antibiotic regimen or IgRT
Antibiotic resistance		Consider a different antibiotic regimen or IgRT
Long term side effects (liver injury, digestive issues etc.)		Consider a different antibiotic regimen, IgRT, or 'antibiotic holiday' if appropriate
IgRT		
Persistent infections due to less efficacy or dose alterations		Close monitoring should always follow any dose adjustments; returning to the last dose that controlled the patient may be required if infections reoccur with a reduced dose. If infections continue to persist, further investigation is warranted to determine the type of infection. Also, if additional infections observed that are not typical of antibody deficiency than combined immunodeficiency should be considered
Cost of therapy/insurance issues		Some patients may experience issues with IgRT depending on their location and medical insurance. Information to alleviate this burden can typically be found on the manufacturer's website for the IgRT product used or local patient organization/advocacy websites
Frequency of infusions/time commitment		Adjustments to the infusion interval can be discussed with the patient, such as easing burden by increasing the interval between infusions for IVIG or SCIG
Needle phobia		Fears can sometimes be addressed through discussion with the patient on IgRT expectation setting and education on IVIG and SCIG therapy – infusions conducted by an HCP or patient caregiver may be preferred
IVIG specific	Venous access	In patients requiring a port for their IVIg, there is an added safety risk with infections and device maintenance. In most cases of venous access issues, SCIg can be recommended before a port
	Side effects (headaches and nausea)	Ensuring the patient is well-hydrated before and during the IV administration and premedication with analgesics and NSAIDs may improve side effects. Alternatively, systemic AEs associated with IVIG are often improved by switching to SCIG
	Missed time from work/school for infusions	Consider switching the patient to SCIG as infusions typically are quicker. Self-administration is also more flexible and allows the patient to infuse at work/school and requires no travel to an infusion center
	Access to infusion center	Consider switching the patient to a home-based treatment, such as IVIG administered by an HCP at home or self-administered SCIG
	Wear-off effects between infusions	Adjustments to reduce the infusion interval can be discussed with the patient for IVIG. Alternatively, switching to SCIG which is infused more frequently can stop wear-off effects
	Local site reactions	Local site reactions tend to improve with subsequent infusions. Many mild local site reactions can also be alleviated by discussion with an HCP who may recommend changes to the infusion (needle length, infusion site, rate/volume per site) or after care (gentle massage, warm/cold compress, OTC topical medications)
SCIG specific	Drug leakage	Reassess ancillary supplies and infusion site; a longer needle or adjusting needle placement may reduce leakage in many cases
	Availability of ancillary supplies and ongoing self-administration support	For those patients on SCIG, additional support can typically be found from the HCP/pharmacy involved in the training. Additional information can be found on the manufacturer's website for the IgRT product used
	Hand strength and coordination	Consider IVIG or SCIG administered via a pre-filled syringe.

AEs, adverse events; HCP, healthcare professional; IgRT, immunoglobulin replacement therapy; IVIG, intravenous immunoglobulin therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter; SCIG, subcutaneous immunoglobulin.

designed to target the specific intracellular pathways identified by the genetic defect [86]. Current targeted therapies under investigation include various monoclonal antibodies, cytokines, and cytokine inhibitors used alone or in combination with traditional immunosuppressant agents or IgRT [71,86]. Future studies are needed to clarify the role of new treatments, their use in relation to specific genetic defects, and ultimately their impact on patient HRQoL.

5. Conclusions

Delayed diagnosis of PID negatively impacts patients' HRQoL, which can persist even after diagnosis and initiation of treatment. Improved awareness of PID, access to specialist centers, and rapid, accurate and cost-effective diagnostic tests can help to further reduce delayed diagnosis. PID awareness and accessibility to testing should be a global initiative. An emphasis should be placed on CVID diagnosis where delay remains the longest and the least changed over recent decades. Although IgRT is associated with high levels of treatment satisfaction in patients with PID, there is no 'one size fits all' approach for treatment administration. Individual patient preferences for IVIG versus SCIG, and pump infusion versus manual push for SCIG, need to be considered in order to maximize patient satisfaction, which will have a beneficial effect on HRQoL. Recurrent moderate viral infections and persistent chronic conditions, such as chronic lung disease, can have a negative impact on HRQoL, even in patients reporting high treatment satisfaction with IgRT and few serious bacterial infections. This represents a key area of focus for improvement in the effective management of patients with PID. Increased acceptance and use of molecular diagnostics should allow for a more targeted approach to optimize and further individualize PID treatment.

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