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Review Article

Cost and impact of early diagnosis in primary immunodeficiency disease: A literature review

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ABSTRACT

Background: New, innovative, costly diagnostic methods for patients with primary immunodeficiencies (PID) demand upfront insight into their potential cost savings and added value for individual patients. As such, high quality, comparable economic evaluations are of utmost importance to enable informed decisions. The objective of this review was therefore to create an extensive overview of current costing studies and potential cost savings of early diagnosis in primary immunodeficiency disease.

Methods: A literature search in PubMed was conducted and studies involving any form of costing study in the field of PIDs were included. Of the included studies, study characteristics, cost parameters and benefits of early diagnosis were extracted and outlined in separate tables.

Results: Twenty two studies met the inclusion criteria and were included in the review. The papers were categorized according to their subject: neonatal screening for severe combined immunodeficiency (SCID), Ig replacement therapies and studies reporting on costs of general or specific PIDs. Within and between these groups variability in reported costing characteristics was observed. In studies that reported cost savings pre- and post-diagnosis, cost savings ranged from 6500 to 108,463 USD of total costs per patient.

Conclusion: This literature review shows that, regardless of what aspect of PIDs has been studied, in nearly all cases early diagnosis reduces health care consumption and leads to better health outcomes for patients with PIDs. We found considerable variability in costing characteristics of economic evaluations of PID patients, which hampers the comparability of outcomes. More effort is needed to create uniformity and define cost parameters in economic evaluations in the field of PIDs, facilitating further prospective research to extensively assess the benefits of early diagnosis.

1. Introduction

Primary immunodeficiency diseases (PIDs) are a heterogeneous group of inherited disorders affecting the immune system [1,2]. Currently, defects in over 400 different genes are known to be associated with the development of immunodeficiencies. Defects within this series of genes may cause impaired functioning or complete absence of essential components of the immune system. The prevalence of PIDs varies by region and is estimated from 1:10,000 to 1:100,000 [3]. Clinical manifestations are characterized by recurrent infections, including infections with opportunistic agents, auto-immune phenomena, failure to thrive and malignancies [4]. Severity of manifestations and complications ranges from mild with relatively little events to severe life-threatening complications.

Treatment of PID patients is dependent on severity of the disease. Conditions as selective IgA deficiency might cause a modest increase in susceptibility to respiratory infections and do most often not require treatment, and there is debate about whether this is an immunodeficiency per se

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[5]. In common variable immunodeficiency disorders (CVID), B-lymphocyte function is impaired resulting in an antibody deficiency, requiring immunoglobulin replacement therapy. Autoimmune complications are usually chronic and require immunomodulating of immunosuppressive therapy. Finally, the more extreme end of the spectrum is comprised of various types of severe combined immune deficiency (SCID) and primary hemophagocytosis, which require hematopoietic stem cell transplantation (HSCT) or gene therapy.

Several studies have highlighted the need for early diagnosis in PID patients [6–10]. Early diagnosis leads to better outcomes and lower costs because of earlier initiation of appropriate treatment. For instance, early diagnosis contributes to timely referral for antibiotic and immunoglobulin treatment in patients with antibody defects, preventing chronic pulmonary disease and additional hospital admissions [11]. Furthermore, early diagnosis in SCID patients facilitates timely referral for hematopoietic stem cell transplantation which is crucial for their survival [8–10,12]. Moreover, evidence suggests that overall mortality in PID patients is significantly higher for those diagnosed at an older age [3], indicating that early diagnosis enables higher survival rates. In practice, delays in correct diagnosis up to decades have been reported, usually due to atypical presentations and the rareness of the diverse PIDs [13].

The need for early diagnosis in PID patients is reflected in the continuous development of new diagnostic tools for evaluation of this group of patients. Current genetic diagnostic methods are effective in providing a definitive diagnosis, but they are relatively expensive and time-consuming [14]. With the growing number of known gene defects associated with PIDs, relevant genetic diagnostic tools now include next-generation sequencing (NGS) based methods. As healthcare resources are limited, it is essential to have detailed overviews of additional value of such relatively expensive diagnostic methods, in terms of effects but also in costs and cost savings. Decision-makers in various countries currently demand such information before reimbursement decisions can be made.

In such economic evaluations, inclusion of a wide range of cost parameters is essential to ensure having valid, complete overviews for decision-makers without over- or underestimating the value of early diagnosis. Data are scarce which often results in combining or extrapolating of data from previous studies.

To ensure having high quality, complete evaluations and to enable early insight in possible cost savings of NGS based methods in early diagnosis of PID patients, it is essential to create an extensive summary of existing costing studies. Therefore, the primary objective of this review is to provide a full overview of all economic evaluations in PID patients and to provide insight in all the costs taken into account. A secondary objective is to study possible cost savings of early diagnosis using the outcomes of this review.

2. Methods

2.1. Search strategy

2.1.1. Database

A literature search in PubMed was conducted in order to identify English articles in English that included cost calculations in any form of PIDs. The database was searched in March 2019 and identified articles published between 1983 and 2019. The reference lists of included articles were screened for any relevant additional studies.

2.1.2. Search terms

The search term consisted of one medical subject heading (MeSH), one subheading and three additional key words. The MeSH term consisted of *"Immunologic Deficiency Syndromes"* combined with subheading *"economics"*. The search term was extended with the following term: *"primary immunodeficien* OR primary immune deficien* AND cost"*

2.1.3. Initial screening

The selection process was performed according to the steps of the PRISMA guidelines [15]. We searched as mentioned for English articles, involving costs of any primary immunodeficiency disease, including costs of available treatments, screening procedures, diagnostic procedures, hospitalization and other direct and indirect costs. Since PID patients are frequently treated with immunoglobulin (Ig) replacement therapy and hematopoietic stem cell transplantation (HSCT) [9,16], we included cost-analyses of Ig therapy and HSCT related to PIDs as well. We included the following types of cost analyses studies. First, we included cost-effectiveness (CEA) studies, describing the ratio of costs of health care to the health benefits [17], and quality of life studies. Second, we included cost-utility analyses (CUA), measuring the ratio of costs to benefits in terms of quality adjusted life years (QALYs), or the number of years lived in full health by patients receiving a specific health intervention [18]. Third, we included cost-minimization analyses, in which the costs of two health interventions with equal effectiveness are compared [19]. Last, we included cost-benefit analyses, in which costs are estimated and compared with the estimated benefits of a health intervention. The most efficient intervention may be selected for implementation in practice.

Inclusion of abovementioned economic evaluation studies depended on the availability of studies on this subject in literature.

All articles with titles matching any of the abovementioned concepts were initially considered, irrespective of detailed criteria such as specific PIDs.

Abstracts of titles that included these concepts were retrieved and screened. When involving diagnostic/screening tools for PIDs, treatment for PIDs and mentioned costs, full-text articles were retrieved for final screening and assessment. The included articles were assessed by two researchers (KE and GF) until consensus was reached.

2.2. Study selection

2.2.1. Inclusion criteria for the final review of articles

- Reports written in English
- Articles published between January 2000 and April 2019
- Articles involving costs of any PID
- Articles involving cost-effectiveness, cost-benefit analyses, cost-minimization analyses and/or cost-utility analyses for treatments specific for PIDs, including immunoglobulin replacement therapy and hematopoietic stem cell transplantation
- Articles involving cost-effectiveness, cost-benefit analyses, cost-minimization analyses and/or cost-utility analyses for screening and/or diagnostic tools for PIDs, such as neonatal or newborn screening for severe combined immune deficiency (NBS-SCID)
- Articles mentioning at least one aspect of costs and/or economic evaluations in the objective of that specific study

2.2.2. Exclusion criteria

- Systematic or literature reviews
- Articles that reported on or mentioned cost-effectiveness but did not show any costs
- Articles that reported on (costs for) treatments, screening tools and/or diagnostic tools that apply for PIDs as well, but did not involve PIDs in that specific study

2.2.3. Analyses

Study characteristics, cost parameters, and benefits of early diagnosis were outlined in separate tables. Study characteristics consisted of general information about the paper, such as study subject and country of origin. Cost parameters were grouped into costs for Ig therapy, HSCT, hospital admission, diagnostics, NBS-SCID, and indirect costs. Benefits of early diagnosis were defined as cost savings or other beneficial

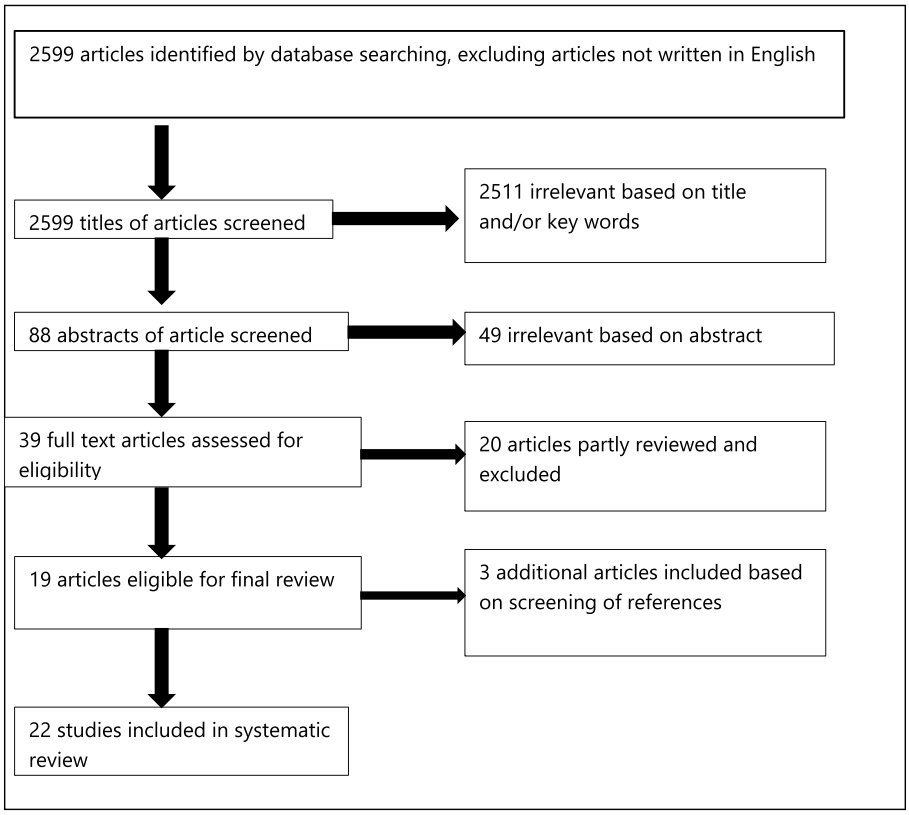

Fig. 1. Flow diagram of selection process according to PRISMA Guidelines.

implications for PID patients attributed to early diagnosis, such as life years saved and deaths averted.

3. Results

3.1. Selection process

The selection process of relevant articles for the final review is shown in Fig. 1. From the initial search, a total of 2775 potentially relevant publications were identified. Articles written in other languages than English were removed from the search results (n = 176). Of the remaining 2599 titles, 2511 were found to be irrelevant based on the key words in the title. Articles were considered irrelevant because they reported secondary immunodeficiencies or other diseases not related to primary immunodeficiencies. A review of the abstracts of the remaining 88 articles identified a total of 39 potentially relevant studies.

After a review of the full articles, a further 20 papers were excluded as they did not meet the selection criteria. Twelve articles reported on cost-effectiveness in the conclusion section of the abstract but did not show data in the results section of the article to support that specific conclusion. Four articles were excluded because the objective or aim of the study did not include an economic evaluation, cost-analysis or cost estimation. Three articles reported on costs for Ig therapy, but those were also related to other diseases or conditions than PIDs. Screening the references of relevant articles resulted in the addition of three more studies. A total of 22 studies were included for the final review. These studies were published between 2005 and 2019, which enables better interpretation of compatibility and economic costs.

3.2. Study characteristics

General study characteristics are shown in Table 1. Studies were categorized according to three main subjects: comparisons of different Ig replacement therapy formulations, newborn or neonatal screening (NBS) for severe combined immunodeficiency, and studies reporting on costs of general or specific primary immunodeficiencies. The available relevant studies regarding economic evaluations for PIDs only comprised the abovementioned subjects.

Nine studies described Ig replacement therapy and were further divided in two categories: comparisons of subcutaneous (SCIG) and intravenous (IVIG) administration routes, and comparisons of different formulations or brands of IVIG [20–28]. All of these studies were cost-

Table 1
Study characteristics.

	Number of studies identified (n = 22)
Subject of study	
Newborn screening for SCID	8
Ig replacement therapy	9
General primary immunodeficiency	5
Study type	
CEA	5
CUA	1
CMA	6
Not specified	10
Perspective	
Society	3
Health/social insurance	4
Health care	7
Not specified	8
Country*	
High income countries	20
Middle income countries	2
Low income countries	–

* According to World Bank Group [54].

minimization analyses, except for three where no study design in terms of economic evaluation was mentioned [21,25,27].

Eight studies involved NBS and four were based on comparisons between "early" and "late" diagnosis and treatment. Kubiak et al. defined "early" as less than 3.5 months of age and late at 3.5 months of age or later, whereas Gardulf et al. defined "early" as less than 6 months and "late" as 6 months or later [29,30]. Clément et al. and Thomas et al. defined "early" as 3 months of age or less and "late" as more than 3 months [31,32]. Other studies compared screening at birth to no screening at all [33–36]. Five articles were either cost-utilization or cost-effectiveness studies with early and late treatment and diagnosis as comparators. Three articles did not report a study design in terms of an economic evaluation [30–32].

Five articles reported on general costs of PID patients. Two aimed to give a global update on clinical outcomes and economic impact of primary immunodeficiencies in different countries [37,38]. Another study by Modell et al. aimed to measure the benefit of different tools designed for early recognition of PID warning signs [39]. Two studies from Iranian origin described the annual costs of disease of CVID patients and annual hospital admission costs [40,41]. None of these articles described a study design in terms of economic evaluations.

Twenty studies reported on data from high income countries [20–39]. Two studies were based on PID-populations from middle income countries [40,41]. No studies from low-income countries were identified.

3.3. Overview of costs

An overview of described costs is demonstrated in Table 2.

3.4. Ig replacement therapy

The Ig replacement therapy studies all describe cost consequences for either IVIG, SCIG, or both. Three articles did not report costs for SCIG because they described IVIG only [21,22,27]. Eight articles describe costs for visits to nurses, physicians, other medical staff or emergency rooms, but composition of these costs differed between studies. They consisted of mean hourly wage for either pharmacist and/or nurse, and infusion time [21–23,28]. Three studies did not further specify the composition of these costs [20,25–27]. Igarashi et al. did not describe costs for staff [24]. Their main focus reflected costs for patients in terms of productivity loss, transportation to hospital, and costs for care provided by relatives [24].

Material costs reflected infusion pumps and additional medical devices needed for administration of immunoglobulin. Two studies did not mention these costs explicitly, but did describe costs for in-hospital intravenous administration [21,22]. Costs for hospitalization consisted of any hospital related costs and reflected bed occupancy, outpatient treatment, and other relevant costs related to Ig treatment.

Costs for diagnostics reflected costs for any diagnostic procedures related to or during Ig treatment and were described by Högy et al. and Fu et al. [20,25] Transportation costs were mentioned by three studies but only Perraudin et al. specified these costs in terms of distance from home to hospital, cost per kilometer, parking costs and public transportation costs for both patients and medical personnel [28].

Productivity loss was based on the average wage of a specific country and hours lost per Ig infusion and was mentioned in four studies [24,26–28]. Overhead costs were costs that could not be assigned to other categories, mentioned by Fu et al. and Perraudin et al. [25,28]

3.5. Newborn screening for SCID

The NBS studies considered cost consequences in two study arms: early versus late hematopoietic stem cell transplantation. Composition of costs as well as definition of 'early' and 'late' differed between studies. All studies measuring cost-effectiveness of implementation of NBS for SCID reported costs for performance of the screening tool itself [29,31,33–36].

McGhee et al. did not include costs of screening since the aim was to identify threshold values of cost, false-negative and -positive rates at which SCID screening would become cost-effective and there was not yet consensus about the best screening method during their study [36]. Gardulf et al. aimed to provide a rationale for NBS by reporting costs for patients that received early versus late HSCT [30].

Hospitalization costs were usually defined as costs for in-patient and out-patient costs in both study arms, including cost of admissions for SCID patients. The level of detail for hospitalization costs differed between studies. For instance, Kubiak et al. did report hospital charges in terms of charges from diagnosis to transplantation and costs from transplantation to 180 days after, but did not provide information on whether costs of visits to medical staff were taken into account, except for pharmacy, intravenous therapy, supplies and laboratory costs [29].

Costs of diagnostics included confirmatory testing of SCID with flow cytometry or other tests and was mentioned in all studies except for Kubiak et al. Productivity impairment was only reported by Chan et al. and Van der Ploeg et al. [33,35]. They also included transportation costs per medical visit. Ding et al measured the economic benefit of averted deaths [34]. Thomas et al. reported costs for screening test as well as costs for qualified personnel [32]. Overhead costs were reported by Clément et al. and Gardulf et al. and refer to costs that could not be assigned to other categories [30,31].

Gardulf et al. divided hospitalization costs for use of the hospital building, for facilities within hospital such as hotel costs, drugs and materials, diagnostic imaging and tests, transportation to and within the hospital, medical staff, and visits to different departments, such as clinical genetics, clinical immunology and transfusion medicine, and overhead costs [30]. The costs were categorized according to in-hospital care and outpatient visits.

3.6. General or specific primary immunodeficiencies

The studies that involved general costs of PID patients provided an overview of costs attributed to PID patients. Sadeghi et al. reported economic burden specifically for common variable immunodeficiency. The studies by Modell et al and Sadeghi et al reported costs pre- and post-diagnosis, whereas Gholami et al. reported costs for hospital admission. All of these studies included costs for (pre)medication. Gholami et al. and Sadeghi et al. included all forms of medication directly related to PIDs and/or associated conditions, such as anti-infective drugs. The studies by Modell et al. included costs for side conditions as well, but did not attribute these costs to medication directly.

All studies included costs for immunoglobulin therapy and costs for visits to medical staff and hospitalizations. Sadeghi et al. and Gholami et al. attributed these costs to hospitalization such as materials, diagnostic testing and laboratory tests. Sadeghi et al. were the only to measure transportation costs to the hospital.

All studies except one reported productivity impairment [41]. Sadeghi et al. described productivity impairment by loss of productive work by the patient using years living with disability and premature death, as well as time spent by relatives to provide the patient with care. Studies of Modell et al. defined productivity impairment as number of school/work days missed.

3.7. Benefits of early diagnosis

Studies that assessed the benefit of early diagnosis and treatment are listed in Table 3. No studies from the Ig replacement group reported on the economic benefits or cost savings of early diagnosis or treatment.

Within the NBS group, benefits of early diagnosis and treatment are measured according to the comparison of costs in early and late hematopoietic stem cell transplantation or the effect of newborn screening compared to no screening. Early transplantation was either defined as

Table 2
Overview of costs.

Cost categories	Martin et al	Fu et al	Beauté et al	Högy et al	Igarashi et al	Kallenberg	Mahadevia et al	Perraudin et al	Connolly & Simoens	Kubiak et al	Chan et al
Ig therapy											
SCIG	X	X	X	X	X			X			
IVIG	X	X	X	X	X	X	X	X	X	X	X
Not specified											
(Pre)medication				X			X				
HSCT											
Early										X	X
Late										X	X
Bone marrow transplantation											
Hospital admission											
(visit to) nurse/physician/ER/other staff	X	X	X	X		X	X	X	X		X
Hospitalization		X	X			X	X		X	X	
Materials	X	X	X	X			X	X			
Transportation (to hospital)			X		X			X			X
Pharmacy costs						X			X	X	
Diagnostics											
Images (X-ray, MRI etc)		X									
Clinical tests/analyses		X									X
Not specified				X							
NBS-SCID											
Reagents											X
Equipment										X	X
Laboratory										X	X
Not specified											
Indirect costs											
Missed school- and workdays/Productivity impairment			X		X		X	X			
Premature death (years of life lost)											
Informal care by relatives					X						X
Overhead costs		X						X			
Clinical conditions affecting PID patients											

Cost categories	Ding et al	Van der Ploeg e al	Thomas et al	McGhee et al	Clément et al	Gardulf et al	Sadeghi et Xal	Gholami et al	Modell et al. (2017)	Modell et al. (2016)	Modell et al. (2011)
Ig therapy											
SCIG											
IVIG				X							
Not specified							X	X	X	X	X
(Pre)medication					X	X	X	X	X	X	X
HSCT											
Early	X	X	X		X	X					
Late	X	X	X		X	X					
Bone marrow transplantation				X							
Hospital admission											
(visit to) nurse/physician/ER/other staff		X	X	X	X	X	X	X	X	X	X
Hospitalization			X	X		X	X	X	X	X	X
Materials			X	X	X	X	X	X			
Transportation (to hospital)							X				
Pharmacy costs											

(*continued on next page*)

Table 2 (*continued*)

Cost categories	Ding et al	Van der Ploeg e al	Thomas et al	McGhee et al	Clément et al	Gardulf et al	Sadeghi et Xal	Gholami et al	Modell et al. (2017)	Modell et al. (2016)	Modell et al. (2011)
Diagnostics											
Images (X-ray, MRI etc)						X					
Clinical tests/analyses				X	X	X					
Not specified	X	X			X		X	X			
NBS-SCID											
Reagents			X		X						
Equipment		X	X		X						
Laboratory		X	X		X						
Not specified	X	X	X								
Indirect costs											
Missed school- and workdays/Productivity impairment		X					X		X	X	X
Premature death (years of life lost)	X										
Informal care by relatives							X				
Overhead costs					X	X					
Clinical conditions affecting PID patients								X	X	X	X

within 3 months of age, at 3.5 months of age or earlier, at 6 months of age or earlier [29–31]. Studies comparing early and late transplantation reported costs in both study arms. Mean total charges for late HSCT ranged from 484,757 to 1,430,000 US dollars. Gardulf et al. calculated the mean cost per child whereas the other two articles described mean total charges for HSCT. In the early HSCT group, mean total charges ranged from 86,179 to 365,785 USD. Cost savings for early versus late transplantation ranged from 109,597 to 1,060,000 USD of total costs per patient.

Other articles focused on early diagnosis by measuring costs and effects of newborn screening versus no screening [33,34,36]. Chan et al. and McGhee et al. reported costs of universal screening for SCID of 22,400,000 and 23,900,000 USD per year, respectively. Additionally, Chan et al. showed an incremental cost-effectiveness ratio (ICER) of 25,429 per life year and 27,907 per QALY. Ding et al. demonstrated an ICER of 35,311 USD per life year saved. Van der Ploeg et al. reported annual health care costs of 439,484 USD higher in a situation with screening compared to no screening. This resulted in a cost-utility ratio of 37,532 USD per QALY gained. Thomas et al. reported difference in mean costs of 59,626 USD but did not report an ICER. All studies concluded that newborn screening is cost-saving and/or cost-effective, except for Thomas et al who did not define benefits of early diagnosis in terms of cost-effectiveness. Chan et al. did this under the assumption that screening costs are 4,22 USD per infant, whereas McGhee et al. assumed a willingness-to-pay of society for every saved QALY of 50,000 USD with a test costing less than five dollars with false-negative rate of 0.9% and false-positive rate of 0.4%.

The studies by Modell et al. reported costs pre- and post-diagnosis and were not specified in terms of PID categories, whereas Sadeghi et al. mentioned costs during the diagnostic trajectory as well (3500 USD per year) in the case of common variable immunodeficiency. Total costs per year pre-diagnosis ranged from 111,053 to 138,760 USD. In the post-diagnosis group, total health costs per year ranged from 30,297 to 128,200 USD and cost savings ranged from 6500 to 108,463 USD per patient per year.

4. Discussion

This review aimed to provide a full overview of economic evaluations regarding PID patients and of all the costs these evaluation studies have taken into account. We found that early diagnosis leads to overall cost savings. We also noted considerable variability in the inclusion of costing characteristics in economic evaluations of PID patients. This variability hampers the comparability of outcomes and decreases the possibility to combine outcomes in health economic modeling or use it across jurisdictions.

The variety in type of costs reported can be illustrated by the fact that not all studies reported a specific economic evaluation. The type of economic evaluation highly depended on study's subjects in the papers. Most articles reported on hospitalization costs, in terms of visits to a physician or other medical staff and costs for transportation to the hospital. Treatment costs were taken into account in all studies. However, the level of detail differed between studies. Some articles reported hourly wage for nurses, whereas others reported costs for home visits by nurses or visits to physicians as well. Hospitalization costs were mainly structured based on physician office visits. The variety in type of economic costs reported might be attributed to the scarcity of economic evaluations in the field of PIDs and the absence of consensus or guidelines on how to these perform economic evaluations.

A second objective of the study was to give a first insight in the possible cost savings of early diagnosis using the outcomes of this review. Again, we noted differences in cost savings depending on the main focus of the study, but all studies agreed that early diagnosis and treatment is beneficial in terms of cost savings and some studies specifically noted the patient advantages, including reduced duration of hospital stays and reduced productivity impairment. Benefits were

Table 3
Cost savings and benefits of early diagnosis.

	Comparators		Cost implications	Other implications	Cost-saving/cost-effective
Kubiak et al	Early (< 3.5 months) HSCT	Late (≥3.5 months) HSCT	Mean total charges for early: $365,785 Mean total charges for late: $1.43 million	NR	Yes
Chan et al	Universal neonatal screening for SCID*	No screening**	Costs of universal screening $22.4 million/year	Universal screening	Yes, assuming screening costs $4.22/infant
		Unaffected***	ICER $25,429/life year and $27,907/QALY.	Life years gained: 880 QALY: 802 No screening Life years lost: 0.000214 QALY: 0.000195	
Ding et al	Newborn screening	No screening	Newborn screening ICER: $35,311 per life year saved	Newborn screening Additional 1.19 cases detected Deaths averted annually: 0.40	Yes
Van der Ploeg et al	Newborn screening	No screening	Newborn screening Total health care costs were $438,009 higher in comparison to a no screening situation. ICER $37,532 per QALY gained	Newborn screening 11.7 QALYs gained Decreased deaths: 0.57 to 0.23 per 100,000 infants.	Yes, treatment costs were $210,000 lower in comparison to a no screening situation.
Thomas et al	Newborn screening Early HSCT (≤3 months)	No screening Late HSCT (> 3 months)	Newborn screening $290,446 in the screening group/ 18 months $230,820 in the control group/18 months Early transplant costs Mean cost of $226,047 Late transplant costs Mean cost of $239,922	NR	Not explicitly reported
McGhee et al	Universal newborn screening	Screening when family history SCID is positive	Costs universal newborn screening $23.9 million/year	Universal newborn screening 760 years of life saved per year per screening	Yes, assuming society's WTP is $50,000 for every saved QALY with a test costing less than $5 with false-negative rate of 0.9% and false-positive rate of 0.4%.
Clément et al	Early (≤3 months) HSCT	Late (> 3 months) HSCT	Charges early HSCT $86,179 Charges late HSCT $195,776	NR	Yes, $56,185–112,370 per case.
Gardulf et al	Early (≤6 months) HSCT	Late (> 6 months) HSCT	Mean costs early HSCT $344,209/child**** Mean costs late HSCT $483,043/child	NR	Yes
Sadeghi et al	Pre-diagnosis	Diagnosis post-diagnosis	Total costs pre-diagnosis/year $134,700 Total costs diagnosis/year $3500 Total costs post-diagnosis/year $128,200	NR	Yes, early diagnosis of the disease can save $6500/annually, because of proper management
Modell et al. 2016, 2017	Pre-diagnosis	Post-diagnosis	Total cost per patient/year without IgG Pre-diagnosis $111,053 Total cost per patient/year with IgG post-diagnosis $25,171 Average annual cost with IgG post-diagnosis $30,000	NR	Yes

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Table 3 (*continued*)

	Comparators		Cost implications	Other implications	Cost-saving/cost-effective
Modell et al. 2011	Pre-diagnosis	Post-diagnosis	Total annual cost per patient pre-diagnosis $138,760 Total annual cost per patient post-diagnosis $30,297	NR	Yes

* Assuming children will go from presymptomatic SCID to HCT directly, representing early diagnosis.
** Assuming diagnosis at time of symptomatic SCID, representing late diagnosis.
*** Children with negative test result.
**** All costs are transformed into US dollars, March 28th, 2019.

expressed in monetary values with clear cost savings, or in deaths averted and life years saved or gained. The greatest cost savings were found within the NBS for SCID and early versus late HSCT groups. Costs of early HSCT were lower than late HSCT in every study, regardless of other parameters. This might be attributed to the fact that late HSCT is related to the development of multiple infections in the case of SCID, increasing the complication rate in HSCT [12,42,43]. Infections before or after HSCT cause extra costs. Moreover, research suggests that cognitive development may be hampered in children undergoing HSCT for SCID, due to isolation and prolonged hospitalization directly after HSCT. When children are undergoing HSCT as early as possible, total health costs may be lower because they do not need to be treated for neurocognitive issues [44]. HSCT before newborns develop symptoms is therefore beneficial and saves costs. The amount of cost savings varied highly between studies. This might be attributed to the fact that different cost categories were taken into account. In the general PID studies, all results show that health costs are higher in the pre-diagnosis stage compared with the post-diagnosis stage. Overall cost savings are attributed to earlier start of appropriate treatment.

A key strength of this review is that it summarizes relevant economic evaluations and cost studies in the field of PIDs. Furthermore, the study provides a clear description of all costs taken into account which provides tools for future research on which cost categories to include within economic evaluations of PIDs.

All studies included in the review were performed in high or middle income countries, according to the World Bank Group. The two studies from middle income countries were from Iranian origin. Theoretically, the higher reported rate of PID in Iran may have influenced cost-effectiveness and cost savings, as the screening costs per case identified will be lower in countries with a higher a priori risk for PID. However, no differences were found in cost-savings between studies from Modell et al. and Sadeghi et al. [37–40]

Another limitation is that most studies in the NBS group were not based on actual implementation and the associated collection of new empirical data. As the results of the studies were based on modeling and assumed costs and effectiveness, researcher bias may have influenced these findings. Most studies were based on US based health models where inputs were drawn from published datasets, existing literature or expert advice. Therefore, generalizability to other health care systems may be limited. Furthermore, our aim was to include an overview of all recently (2005–2019) published cost studies regarding diagnosis and treatment of PIDs. However, the field of PID diagnostics has greatly changed and improved throughout these years, especially due to the application of next-generation sequencing in PID diagnostics [45–48]. This may have influenced our results regarding the outcomes of economic evaluations and early diagnosis.

Also, all papers describing HSCT in PIDs were focused on SCID. However, HSCT is becoming increasingly successful for a growing range of non-SCID PIDs, such as chronic granulomatous disease, monogenetic cases of CID such as CD40 ligand deficiency, and complex immune dysregulation disorders [9,49–52]. However, cost-effectiveness studies are – to our knowledge – not yet available for HSCT for these non-SCID PIDs – but are essential in future systematic reviews on economic evaluations regarding PIDs.

Other factors that may have influenced the outcomes are related to the use of Ig replacement therapy. Patients with different type of PID, such as CVID or XLA, are treated with Ig replacement therapy [53]. However, duration of disease and thus the time span of treatment may differ between patient groups. Naturally, this may have consequences related to overall Ig treatments costs in our review. Therefore, results regarding Ig therapy costs should be interpreted with caution.

In conclusion, although we found no uniformity in the types of costs reported per study, early correct diagnosis of PID patients led to overall cost savings in all studies reported in this overview paper. The expected drop in costs and turn-around-time for more sophisticated and accurate NGS methods for genetic diagnostics will determine its implementation

as a routine diagnostic test in well-selected patient cohorts, including PIDs. Further research is needed to explore which costs are essential in economic evaluations regarding early diagnosis of primary immunodeficiencies. Also, future economic evaluations for HSCT should focus on other diseases than SCID as well, such as CGD. Only by improved data collections and improved cost analyses, combined with progressively enhanced NGS data acquisition, clear guidelines can be developed for future cost reviews involving primary immunodeficiencies.

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