The case for a national service for primary immune deficiency disorders in New Zealand

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ABSTRACT

Primary immune deficiency disorders (PIDs) are rare conditions for which effective treatment is available. It is critical these patients are identified at an early stage to prevent unnecessary morbidity and mortality. Treatment of these disorders is expensive and expert evaluation and ongoing management by a clinical immunologist is essential. Until recently there has been a major shortage of clinical immunologists in New Zealand. While the numbers of trained immunologists have increased in recent years, most are located in Auckland. The majority of symptomatic PID patients require life-long immunoglobulin replacement. Currently there is a shortage of subcutaneous and intravenous immunoglobulin (SCIG/IVIG) in New Zealand. A recent audit by the New Zealand Blood Service (NZBS) showed that compliance with indications for SCIG/IVIG treatment was poor in District Health Boards (DHBs) without an immunology service. The NZBS audit has shown that approximately 20% of annual prescriptions for SCIG/IVIG, costing $6M, do not comply with UK or Australian guidelines. Inappropriate use may have contributed to the present shortage of SCIG/IVIG necessitating importation of the product. This is likely to have resulted in a major unnecessary financial burden to each DHB. Here we present the case for a national service responsible for the tertiary care of PID patients and oversight for immunoglobulin use for primary and non-haematological secondary immunodeficiencies. We propose that other PIDs, including hereditary angioedema, are integrated into a national PID service. Ancillary services, including the customised genetic testing service, and research are also an essential component of an integrated national PID service and are described in this review. As we show here, a hub-and-spoke model for a national service for PIDs would result in major cost savings, as well as improved patient care. It would also allow seamless transition from paediatric to adult services.

Primary immune deficiency disorders (PIDs) are rare genetic defects resulting in compromised host defences.[1] Consequently, affected patients are susceptible to recurrent and severe infections, as well as autoimmunity and malignancy as a result of immune dysregulation.[2-5] The severity of PIDs range from asymptomatic IgA deficiency, to life-threatening infections from severe combined immune deficiency (SCID). The prevalence of these disorders vary, from being relatively common (1:300) for IgA deficiency, to extremely rare conditions, some of which have not been identified in New Zealand (population: 4.4M).[1,6]

It is imperative these patients are identified in a timely manner.[7] Early identification of these conditions, and establishing appropriate treatment, may prevent or mitigate disabling complications such as bronchiectasis. If identified and treated promptly, the majority of patients can lead a full and active life with minimum morbidity.[8]

Severe PIDs, such as SCID are a paediatric emergency and require immediate referral to Paediatric Immunology at Starship Children's Hospital, Auckland (Starship) for evaluation and treatment. In other cases, there is less urgency, such as patients with IgA deficiency suffering from upper respiratory tract infections. The potential severity of a disorder may not be apparent in the early stages, but there may be rapid deterioration if not identified and referred promptly. This occurs in patients with SCID,

who may initially be well until they contract CMV or Parainfluenza 3 viral infections, making subsequent management very difficult. Similarly, patients with X-linked lymphoproliferative disease can remain well until they suffer a catastrophic EBV infection.[9] In this example, early identification of males carrying the genetic defect, and pre-emptive bone marrow transplantation, is potentially curative with a much improved prognosis.[10] These examples underscore the need for timely evaluation by specialists in clinical immunology.

Once diagnosed, PID patients should be under the long-term care of an immunology service. This is essential, as there are many aspects of ongoing patient care which require regular input from an immunologist. Some patients may have persistent infections, while others may develop autoimmune and inflammatory sequelae. Furthermore, an immunologist is in the best position to undertake genetic studies, which can have profound benefits to the patient and the family.

Currently, there is a serious maldistribution of clinical immunologists, and particularly immunopathologists, in New Zealand. Most immunologists work in Auckland. The Immunology Department at Auckland District Health Board (ADHB) employs seven part-time consultants, and one fellow. There are three part-time paediatric immunologists at Starship. Two clinical immunologists, and three allergy specialists, are exclusively in private practice in Auckland. The only public paediatric immunology service is based at Starship. also in Auckland.

Christchurch and Wellington have two adult immunologists. A part-time paediatric allergist works in Wellington. The adult Immunology Department at ADHB offers a monthly outreach clinic in Whangarei. One part-time immunologist conducts monthly clinics at Waikato Hospital. The Immunology Department at ADHB has contracts to review a modest number of patients from other hospitals within the Auckland area, and other DHBs in the upper North Island. Other cities, as well as other hospitals in Auckland, do not have a visiting adult immunology service. Visiting paediatric immunology outreach clinics are conducted in Hamilton, Rotorua, Tauranga and Invercargill.

As a consequence of the maldistribution of public hospital immunologists, some adult PID patients, and many with non-haematological secondary immunodeficiencies, have not had the opportunity to undergo a thorough immunology review, and regular follow-up. Current contractual arrangements between DHBs may result in financial disincentives for patient referrals for subspecialty reviews.[11] For example, patients referred from DHBs without a contract with ADHB may be seen, but no funding follows these consultations, which may disadvantage local patients within the ADHB catchment area. By default, some adult patients remain under the care of general physicians or haematologists. In some cases, long-term subcutaneous or intravenous immunoglobulin (SCIG/IVIG) replacement has been initiated and continued without immunology consultation. The cost of SCIG/IVIG over a lifetime is more than $1M and is funded by the local DHB. As shown below, in many cases the inappropriate use of SCIG/IVIG has resulted in a major unnecessary financial burden to individual DHBs.

In this Viewpoint, we present the case for a national service for patients with PIDs. A national PID service would significantly reduce healthcare costs, and more importantly improve patient care. This is similar to HIV medicine, where patients under the care of physicians with appropriate training and experience have significantly better outcomes.[12] We describe some areas where input from an immunologist would make a significant difference to patient management, and would also substantially reduce healthcare expenditure.

Hypogammaglobulinemia/ Common Variable Immunodeficiency Disorder and SCIG/ IVIG treatment

Patients presenting with hypogammaglobulinemia are a common clinical scenario. Within the spectrum of hypogammaglobulinemia, it is very important that patients with Common Variable Immunodeficiency

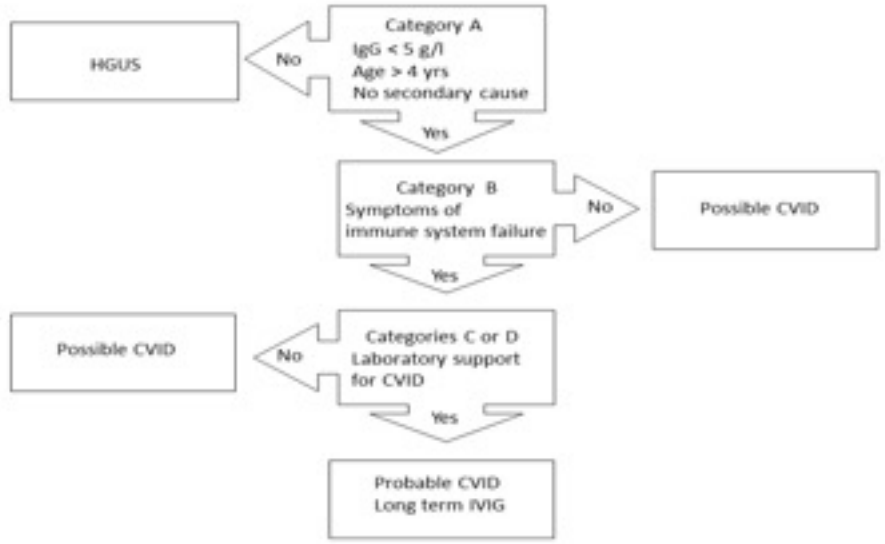
Table 1: Ameratunga et al (2013) diagnostic and treatment criteria for CVID.[14,15]

Category A: Must meet all major criteria
Hypogammaglobulinemia IgG <5 g/l[4]
No other cause identified for immune defect[17]
Age >4 years[2]
Category B: Sequelae directly attributable to immune system failure (ISF) (1 or more)
Recurrent, severe or unusual infections
Poor response to antibiotics
Breakthrough infections in spite of prophylactic antibiotics
Infections in spite of appropriate vaccination eg HPV disease
Bronchiectasis and/ or chronic sinus disease
Inflammatory disorders or autoimmunity[18]
Category C: Supportive laboratory evidence (3 or more criteria)
Concomitant reduction or deficiency of IgA (<0.8 g/l) and/or IgM (<0.4 g/l)[3,19]
Presence of B cells but reduced memory B cell subsets and/ or increased CD21 low subsets by flow cytometry[20,21]
IgG3 deficiency (<0.2 g/l)[22,23]
Impaired vaccine responses compared to age-matched controls[24]
Transient vaccine responses compared with age-matched controls[25]
Absent isohemagglutinins (if not blood group AB)[26]
Serological evidence of significant autoimmunity eg, Coombes test
Sequence variations of genes predisposing to CVID eg, TACI, BAFFR, MSH5 etc[27,28]
Category D: Presence of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty, in the context of Category A and B criteria)
Lymphoid interstitial pneumonitis[29]
Granulomatous disorder [30,31]
Nodular regenerative hyperplasia of the liver[32,33]
Nodular lymphoid hyperplasia of the gut[34]
Absence of plasma cells on gut biopsy[35,36]

Disorder (CVID) are identified at an early stage. CVID is the most common symptomatic PID in adults, with a prevalence of approximately 1:25 000.[6] Symptoms can begin in adulthood in many patients.[13] Failure to identify and treat CVID patients may place them at risk of bronchiectasis and/or life-threatening infections, including meningitis and septicaemia. Once identified, patients with CVID should receive long-term subcutaneous or intravenous immunoglobulin (SCIG/IVIG) replacement. Our recently published diagnostic criteria for CVID will allow a diagnosis of probable CVID to be made with more precision (Table 1).[14] CVID is no longer a diagnosis of exclusion. Treatment guidelines are closely linked to diagnostic categories (Figure 1).[15,16]

As part of the clinical evaluation, predisposing factors for infections should be thoroughly assessed. It is possible the hypogammaglobulinemia is not the dominant cause for infections.[14] In our experience, treatment of conditions such as chronic tonsillitis or chronic sinus disease may result in major improvement in the frequency of infections in some patients with hypogammaglobulinemia, without the need for SCIG/IVIG replacement.

Figure 1: Treatment algorithm for CVID (Ameratunga et al 2013).[14]



Given the very high cost of SCIG/IVIG, all PID patients should have an immunology evaluation prior to commencing treatment. We also strongly recommend that patients already placed on long-term SCIG/IVIG for PID should be regularly reviewed by an immunologist. We have recently identified an adult patient who had been on long-term IVI,G but was subsequently able to discontinue treatment as he had recovered from "transient hypogammaglobulinemia of infancy" as an adult. As a result, we were able to successfully discontinue his IVIG. He remains well, with no increase in infections with an IgG of 6.5 g/l (7-14 g/l).

Our diagnostic criteria may allow CVID to be confirmed, without the need to stop SCIG/IVIG in some patients, particularly if they have characteristic histological features (Table 1, category D).[16] This could reduce the need to stop SCIG/IVIG treatment to undertake vaccine challenge responses, which can take several months. The patient may be vulnerable to sepsis during this time. Equally, these criteria may identify individuals who can safely discontinue SCIG/IVIG treatment permanently, if they have minimal symptoms, with normal memory B cells and normal plasma cells on gut biopsy (Table 1).

Patients must meet all major criteria in Category A for consideration of CVID. Category B confirms the presence of symptoms indicating immune system failure (ISF). Patients must be symptomatic to have CVID. To qualify as having probable CVID, patients must have supportive laboratory evidence of immune system dysfunction (Category C) or characteristic histological lesions of CVID (Category D). Patients with mild hypogammaglobulinemia (IgG >5 g/l) are termed hypogammaglobulinemia of uncertain significance (HGUS). Patients meeting Category A criteria but not other criteria are deemed to have possible CVID. Most patients with probable CVID are likely to require IVG/SCIG. Some patients with possible CVID will require SCIG/IVIG but most patients with HGUS are unlikely to need IVIG/SCIG replacement. We have suggested HGUS patients are categorised based on their symptomatic state ie sHGUS or aHGUS. Some patients with bronchiectasis with HGUS will need to be treated with SCIG/IVIG irrespective of vaccine responses.[16]

It may not be initially clear if a patient presenting with hypogammaglobulinemia has a primary or a secondary immune deficiency. We have shown that our diagnostic criteria can also be useful in identifying patients with secondary immunodeficiencies.[37-39] These criteria may also help in complex situations where an underlying primary immunodeficiency is aggravated by a secondary immunodeficiency, such as an anticonvulsant drug.[38] Several other patients with secondary hypogammaglobulinemia have also been able to discontinue IVIG replacement uneventfully and remain well. These patients were commenced

on IVIG by other services and successful discontinuation has resulted in significant cost savings.

Once patients are placed on long-term SCIG/IVIG treatment, they need regular immunology review. Patients residing outside centres with immunology units would share their care with local paediatricians and physicians, in the case of adult patients. The frequency of the follow-up visits to immunologists will depend on the individual patient and their disorder. SCIG/IVIG treatment usually results in significant improvement of the frequency and severity of infections, but may not alter the risk of inflammatory disorders or malignancy. IVIG, and to lesser extent SCIG, can cause adverse effects,[40] and having an immunologist involved in the patient's care can facilitate timely review and management of any complication from treatment. Other options, including an alternative immunoglobulin product, may need to be considered. These decisions are best made by immunologists, who are thoroughly familiar with alternative SCIG/IVIG preparations, which may need to be imported for a specific patient.

Some patients with CVID have severe antibiotic allergies because of immune dysregulation. Managing these patients can be challenging and requires the expertise of an allergy/ immunology specialist. Diagnostic evaluation may include skin testing and drug challenges to confirm remission. Acute antibiotic desensitisation may be needed for management of severe bacterial infections. Again, this service is available in specialist immunology units.

Patients with CVID are at risk of chronic upper and lower respiratory tract suppuration. We routinely share their care with the respiratory and ORL services. Many patients require functional endoscopic sinus surgery for chronic sinus disease. Having access to respiratory and ORL specialists with experience in PIDs is likely to improve outcomes in these medically complex patients. These are strong clinical arguments for placing patients with PIDs under the care of immunologists, which may be best done through a national service for PIDs. This would ensure uniformity of clinical care.

The New Zealand Blood Service (NZBS) audit of SCIG/IVIG use

Perhaps the strongest economic argument for a national PID service comes from a recent SCIG/IVIG audit conducted by the New Zealand Blood Service (NZBS, Blood Issues 28, October 2015, http://www.nzblood.co.nz/assets/Transfusion-Medicine/Blood-Issues-Newsletter-No-28-October-2015.pdf). The case notes of patients receiving SCIG/IVIG in 2012/2013 from 10 DHBS were reviewed. Access to old notes was sometimes difficult, given that some patients have been on IVIG for decades. Where notes were not available, the prescribing doctor was contacted for further information. This audit was undertaken by nursing staff in each NZBS area. NZBS has indicated there are limitations to the audit. It is likely there was some observer inconsistency. The audit did not determine if the patient was reviewed by an immunologist. Furthermore, the case notes were not critically reviewed by an immunologist and subtle nuances, such as responses to alternative treatments, were not recorded.

The cost of SCIG/IVIG is $88 per gram, and the total cost to the New Zealand taxpayer is $29M per year. The NZBS determined compliance of SCIG/IVIG use against criteria published in the UK and Australia. The audit uncovered inconsistencies in the use of IVIG within the ten DHBs it audited (Tables 2 –5). It can be seen there was a high compliance rate in Auckland for PID patients, but relatively poor rates in some of the smaller DHBs without access to immunology services.

It is also clear that compliance for treating secondary immunodeficiencies with SCIG/IVIG is poor in most DHBs (Table 5). The poor compliance for secondary immunodeficiencies may simply reflect a lack of referral to immunology services, including ADHB. Most patients with non-haematological secondary immunodeficiencies are likely to benefit from an immunology review. Patients with drug induced immunodeficiencies for example may improve if the causative drug is identified and discontinued.[41] As

Table 2: NZBS audit showing major indications for SCIG/IVIG.

Diagnosis	% total grams use	Number of patient episodes and % of all episodes	NBA guideline		NHS guideline	
			Number and % patients complying with qualification criteria	Number and % patients complying with review criteria	Number and % patients complying with qualification criteria	Number and % patients complying with review criteria
Primary Immunodeficiency	30%	172 (19.5%)	152 (88%)	No criteria	152 (88%)	No criteria
Secondary Immunodeficiency	18%	186 (21%)	83 (45%)	136 (73%)	9 (5%)	165 (89%)
CIDP	16%	65 (7.4%)	47 (72%)	49 (75%)	25 (38%)	50 (77%)
ITP	6%	98 (11.1%)	92 (94%)	98 (100%)	90 (92%)	95 (97%)
Guillain-Barré Syndrome	6%	65 (7.4%)	48 (74%)	58 (89%)	49 (75%)	52 (80%)
Other conditions	24%	297 (33.6%)	219 (74%)	200 (67%)	242 (81%)	221 (74%)
Total evaluable patients episodes	100%	883 (100%)	641 (73%)	541 (76%)	567 (64%)	583* (82%)

NBA: National Blood Authority of Australia NHS: National Health Service UK. ~~CDP:~~ chronic inflammatory demyelinating peripheral neuropathy. ITP: immune thrombocytopenia. Qualification criteria refer to the NBA and NHS guidelines, while the review criteria refer to ongoing clinical reviews.

noted above, the immunology service at ADHB has been able to discontinue IVIG in several patients with secondary immunodeficiencies. The audit also uncovered patients who had been treated with IVIG for conditions such as autism and chronic fatigue syndrome, which are not supported by either the Australian or UK guidelines.

From these tables we have calculated that $6M of immunoglobulin prescriptions per year do not comply with UK or Australian guidelines.

The current approval process for SCIG/IVIG treatment

We are very concerned about the current approval process for IVIG/SCIG treatment. At present, the NZBS has to vet SCIG/IVIG requests for immunodeficiencies. Each requesting clinician contacts the regional blood service for approval for IVIG/SCIG. Guidelines for IVIG/SCIG are not strictly enforced by the NZBS. It is currently not a requirement for patients with primary or non-haematological secondary immunodeficiencies to have been reviewed by a clinical immunologist. Each blood service may not be in a position to determine the appropriateness of the request, and it is likely there are inconsistencies in the approval process. This may explain use of IVIG/SCIG for disorders such as autism and chronic fatigue syndrome. We feel decisions on IVIG/SCIG usage in primary and non-haematological secondary immunodeficiencies should be made by clinical immunologists after thorough clinical evaluation of these patients. The NZBS strongly supports the creation of a national service for PIDs with oversight for the prescription of SCIG/IVIG for PIDs and non-haematological immunodeficient patients (Dr Peter Flanagan, Director NZBS, personal communication, October 2015). Patients with secondary immunodeficiencies from haematological disorders should be reviewed a haematologist. A national PID service is likely to result in a fairer and more transparent process for IVIG/SCIG prescriptions.

We accept that there may be potential inaccuracies with retrospective review of patient notes. However, we are confident there will be substantial financial benefits to each DHB if a national PID service was established with oversight for immunoglobulin prescriptions for primary and non-haematological secondary immunodeficiencies. It is also likely hospitalisation costs would be reduced if patients were under the care of a clinical immunologist. These fiscal benefits are in addition to the improvement in clinical care described previously.

Table 3: NZBS audit showing use of SCIG/IVIG by various District Health Boards in New Zealand.

DHB	Intragam P use pa (g)	Audit episodes	Population*	Intragam P use pa (g) per 1000 population	Average age (years)	Average weight (kg)	Status
Auckland	56,010	257	404,619	138	29	52	audited
Canterbury	31,995	141	466,407	69	39	59	audited
Capital and Coast	30,522	119	266,658	114	43	68	audited
Counties Manukau	12,351	75	433,086	29	44	62	audited
Hawkes Bay	7,260	27	148,248	49	40	66	audited
MidCentral	9,630	41	158,841	61	45	70	audited
Northland	8,349	35	148,440	56	36	61	audited
Southern	21,063	80	286,224	74	53	67	audited
Tairawhiti	2,250	7	44,463	51	40	54	audited
Waikato	28,362	109	339,192	84	50	71	audited
Bay of Plenty	17,343	73	194,931	89			not audited
Hutt Valley	5,571	21	136,101	41			not audited
Lakes	7,251	30	98,319	74			not audited
Nelson Marlborough	5,787	26	130,062	44			not audited
South Canterbury	666	5	53,877	12			not audited
Taranaki	5,043	22	104,277	48			not audited
Wairarapa	2,889	8	38,613	75			not audited
Waitemata	8,655	73	481,611	18			not audited
West Coast	855	4	31,326	27			not audited
Whanganui	2,583	9	62,211	42			not audited
In audit	207,792	891					
Audited %	79%	77%					
Not audited	56,643	271					

* based on population data 2012

Hereditary angioedema (HAE)

Hereditary angioedema (HAE) is a rare disorder resulting from mutations of the C1 inhibitor or FX11 genes.[42] Patients are predisposed to recurrent angioedema and abdominal pain. Urticaria is absent. The vast majority of patients with C1 inhibitor deficiency have reduced complement component 4 levels, as well as reduced C1 inhibitor function, and/or antigen levels. HAE is currently considered a PID, even though predisposition to infections and autoimmunity are not a major feature of the disorder.

Standard treatment in New Zealand for C1 inhibitor deficiency is androgens (Danazol or Stanozolol). Fibrinolytic inhibitors have a minor role in management. Patients suffering an acute attack require infusions with purified or recombinant C1 inhibitor or Icatibant, which ~~will soon be~~ funded. Treatment of an acute attack with purified C1 inhibitor costs approximately $2,500, plus costs of hospitalisation. Preventing attacks with attention to triggering factors and androgen therapy may result in major cost savings to healthcare services.

There is also a strong economic argument to allow HAE patients to self-infuse C1 inhibitor to reduce the costs of hospitalisation.[43] This is similar to haemophilia, where patients are encouraged to self-medicate. Early treatment of angioedema attacks reduces morbidity. C1 inhibitor is

Table 4: NZBS audit showing compliance in treating PIDs. The NZBS data do not subcategorise the specific type of PID. Therefore, it is difficult to determine if this is the expected number of PID patients in New Zealand who should be receiving SCIG/IVIG.

DHB	NBA compliant		NHS compliant		Overall use	
	grams	patients	grams	patients	grams	patients
Auckland	23,952 (100%)	70 (100%)	23,940 (100%)	69 (99%)	23,952	70
Canterbury	8,043 (100%)	22 (100%)	8,043 (100%)	22 (100%)	8,043	22
Capital and Coast	9,012 (91%)	22 (92%)	9,588 (96%)	23 (96%)	9,948	24
Counties Manukau	876 (81%)	6 (86%)	1,086 (100%)	7 (100%)	1,086	7
Hawkes Bay	972 (82%)	2 (67%)	1,188 (100%)	3 (100%)	1,188	3
MidCentral	1,650 (100%)	4 (100%)	1,650 (100%)	4 (100%)	1,650	4
Northland	4,386 (90%)	12 (92%)	4,386 (90%)	12 (92%)	4,854	13
Southern	1,563 (30%)	5 (36%)	1,563 (30%)	5 (36%)	5,211	14
Waikato	3,627 (63%)	9 (60%)	2,856 (49%)	7 (47%)	5,790	15
Overall	**54,081 (88%)**	**152 (88%)**	**54,300 (88%)**	**152 (88%)**	**61,722**	**172**

Table 5: NZBS audit showing compliance with SCIG/IVIG use in secondary immunodeficiencies. The audit did not determine if patients had consulted with a clinical immunologist.

DHB	NBA compliant		NHS compliant		Overall use	
	grams	patients	grams	patients	grams	patients
Auckland	3,396 (62%)	23 (56%)	987 (18%)	3 (7%)	5,448	41
Canterbury	3,954 (67%)	18 (67%)	384 (6%)	2 (7%)	5,928	27
Capital and Coast	912 (11%)	5 (14%)	363 (4%)	1 (3%)	8,451	37
Counties Manukau	1,749 (59%)	8 (53%)	0 (0%)	0 (0%)	2,988	15
Hawkes Bay	852 (47%)	2 (67%)	0 (0%)	0 (0%)	1,815	3
MidCentral	624 (39%)	3 (43%)	0 (0%)	0 (0%)	1,608	7
Northland	531 (100%)	3 (100%)	228 (43%)	1 (33%)	531	3
Southern	2,277 (67%)	13 (57%)	690 (20%)	2 (9%)	3,405	23
Waikato	2,037 (29%)	8 (27%)	0 (0%)	0 (0%)	6,912	30
Overall	**16,332 (44%)**	**83 (45%)**	**2,652 (7%)**	**9 (5%)**	**37,086**	**186**

more effective when used early, before the onset of severe gastrointestinal edema.[44] Laryngeal attacks require immediate treatment with C1 inhibitor. The ability of self-infuse C1 inhibitor has substantially reduced healthcare costs in Canada. Having a national PID service could significantly reduce costs by providing clinical advice on how to prevent acute attacks and by training patients to self-administer C1 inhibitor at home.[45] A national service would also provide a uniform approach to the management of these patients throughout the country.

Genetic testing

In recent years there have been rapid advances in the understanding of PIDs. The majority of PIDs are a consequence of monogenic disorders. Over 260 causative or predisposing genetic defects have been identified in PID patients.[1] With the notable exception of CVID, genetic tests play a major role in patient management (Table 6).[46-48] As well as confirming the diagnosis, these tests allow family studies, and may allow prevention of PIDS with prenatal diagnosis and pre-implantation genetic diagnosis.[47]

Table 6: Advantages of molecular analysis for PID diagnosis. The original case descriptions can be found in our review on PID genetic testing.[47]

Diagnosis of PID
Distinguishing genetic from acquired disorders
Confirming the clinical diagnosis
Identifying novel presentations of PIDs
Identifying atypical presentations of PIDs
Urgent diagnosis in infancy where conventional diagnostic tests are unreliable
Treatment
Assisting treatment decisions
Gene therapy- identifying those who may benefit from gene based therapy
Prognosis
Determining long-term outcome
Pre-symptomatic testing
Where presymptomatic diagnosis (at any age) is not possible with protein based tests
Early identification of disorders which present later in childhood
Screening
Cascade screening of at-risk relatives
Population based screening
PID prevention
Prenatal diagnosis
Pre-implantation genetic diagnosis
Research
Characterising the role of molecules in cellular function
Assisting with the classification of primary immunodeficiency disorders
Identification of new genetic defects including animal models

Genetic testing should now be considered the standard of care for most monogenic PID disorders (Table 6).

Genetic testing for PIDs has been undertaken in New Zealand for over 20 years.[49] In the last decade, the immunology laboratory at Auckland Hospital has offered a customised genetic service for patients with PIDs.[48] This service is accredited by the New Zealand laboratory accreditation agency, IANZ, and is publically funded for New Zealand citizens and residents. We currently offer full-length genomic (Sanger) sequencing for any published PID gene. The service offers a rapid turn-around, with results typically being available within 2–3 weeks, or sooner for urgent cases. This service is a cost-effective solution for a small, developed country.[47] Genetic testing for PIDs is also available in Christchurch.

The customised genetic testing service is of particular significance to Māori, as it conforms to Tikanga Recommended Best Practice.[47] It removes the need to send samples to overseas laboratories. Long-term storage of samples in overseas research laboratories may be of concern to some Māori.

Currently, several regional and national services based in Auckland depend on two scientists for rapid sequencing of PID genes. These include adult and paediatric immunology (PID syndromes), adult and paediatric rheumatology (autoinflammatory disorders), adult and paediatric haematology (haematophagocytic lymphohistiocytosis, HLH syndromes), and adult and paediatric

nephrology (atypical haemolytic uremic syndromes) services. It would seem appropriate to integrate a PID testing service into a national immunology service. This would not preclude other laboratories from offering PID genetic testing for local patients.

Immunopathology

Immunopathology is a subspecialty within clinical pathology. Laboratory testing for immunological disorders is complex. Many assays have not been automated, and a high level of operator skill is required for successful completion and interpretation of results.

While immunopathology is broader than PID testing, a national service could allow immunopathology supervision of laboratories with intermittent visits. Alternatively, a national immunopathology service could be considered separately. Considerable immunopathology expertise exists in Christchurch, which would be the hub for the South Island, and provide specialised testing nationally for specific autoimmune disorders.

PID research

New Zealand is currently involved in several PID research projects. Currently, most patients with CVID are enrolled in a long-term project evaluating their clinical features and outcomes. Over 80% of known CVID patients in New Zealand are part of this project. All patient notes and laboratory results have been thoroughly audited as part of the study. As seen in the NZBS audit, we believe such a thorough review should be undertaken for all PID patients on SCIG/IVIG, either as part of the study or as part of ongoing clinical care. Having such a database (once approved by the Ministry of Health ethics committee and current participants) linked to a national service would ensure patients are not lost to follow-up, and they continue to receive the appropriate care. Research is an essential part of a national PID service.

In addition, New Zealand has a long-term hypogammaglobulinemia study for patients not on SCIG/IVIG. This study seeks to identify the long-term prognosis for these patients. This cohort will also be used to validate CVID diagnostic criteria. Having a better understanding of the natural history of hypogammaglobulinemia is likely to save the health service large sums of money, as not all patients with hypogammaglobulinemia have CVID, and not all require SCIG/IVIG, especially if they are symptomatically well. Again, the project could be linked to a national PID service to ensure patients from around the country are enrolled and are not lost to follow-up.

The laboratory at Auckland Hospital has been undertaking whole exome sequencing (WES) as part of a research project. CVID families with more than one affected relative have been invited to join the WES project seeking to identify new genes. The program to date has identified two new genes associated with CVID-like disorders.[50] Identification of the causative gene has profound implications for the patient and family members as discussed above (Table 6). Again, having a national PID service will ensure uniform access to research studies such the ones described here.

Discussion: advantages (and disadvantages) of a national service for patients with PID

A national service for patients with PID has many advantages (and a few disadvantages) as described above. Importantly, it will allow thorough and timely evaluation of patients with suspected primary and non-haematological secondary immune deficiency disorders. It may be difficult to distinguish between a primary and secondary immune deficiency until the patient is reviewed by a clinical immunologist. An immunology review will result in appropriate testing and a confident diagnosis of a PID (or secondary immunodeficiency). Careful evaluation of these patients will result in major savings from more effective use of SCIG/IVIG. As outlined above, many patients with mild-moderate hypogammaglobulinemia remain well once other predisposing factors for recurrent infections are treated. These patients may not need to be treated with SCIG/IVIG. They will of course require long-term follow-up, as some will develop a symp-

tomatic immune deficiency disorder over time. We believe these decisions, which carry substantial clinical risk, should only be made by an immunologist. If a secondary immune deficiency is identified,[9,37] the patient can be treated or referred to the appropriate service. This would minimise the inappropriate use of IVIG, as seen in Table 5. This would result in more judicious and equitable use of SCIG/IVIG throughout New Zealand.

There has been a substantial increase in the use of SCIG/IVIG in recent years. The NZBS estimates there has been a 10.4% annual increase in demand for SCIG/IVIG over the last decade. As shown in Table 5, it is likely inappropriate use of IVIG has also contributed to the increased use of SCIG/IVIG in New Zealand. As a result, supplies of Intragam P, manufactured from local plasma donors, have not been able to meet this increased need. The NZBS has confirmed that New Zealand is no longer self-sufficient in the production of SCIG/IVIG. The NZBS has had to import SCIG/IVIG preparations, manufactured from overseas donors, at considerable cost to the taxpayer. This underscores the urgency to establish a national PID service which has oversight for SCIG/IVIG use in primary and non-haematological secondary immunodeficiencies. We would expect a national PID service to clinically review all primary and non-haematological secondary immunodeficient patients prior to the use of SCIG/IVIG. This will have the added clinical benefit of optimising management of these patients. SCIG/IVIG treatment decisions are by consensus at ADHB. We have shown how consensus decisions can work effectively in clinical practice.[51] This would reduce the risk of inconsistent decisions being made by local NZBS services. We are very confident substantial immediate and sustained cost savings will result from the establishment of a national PID service with oversight for SCIG/IVIG prescriptions for immunodeficiencies.

A national PID service will secure the future of the customised genetic testing service, which has significantly improved health outcomes, and has also resulted in considerable cost savings to the New Zealand taxpayer. After intense counselling, several families are considering preimplantation genetic diagnosis, which will result in cost savings as well as alleviating suffering in future generations.

The future of genetic testing lies in the development of NGS-based gene panels. Gene panels are now offered by many diagnostic laboratories in the US.[52] A diagnostic service, based on targeted next-generation sequencing (NGS) is being developed at LabPlus. Using targeted WES as a rapid screening method for known PID genes is a potential strategy, which could be much cheaper than sequentially testing multiple genes. Gene panels could be deployed when the genetic defect is not clear from the history or protein based laboratory testing. The development of functional studies is an essential part of this program.

If the causative gene is not clear from the initial targeted NGS panel, WES for gene discovery could be deployed in the context of a research program. WES has a major role in identifying novel genetic defects in patients with unknown clinical conditions. A recent study from the NIH identified the genetic defect in 24% of patients with undiagnosed disorders.[53] These research assays are best performed within the framework of a national clinical immunology service with access to protein-based and functional studies.

Newborn screening for SCID will be implemented in New Zealand in the near future. Prompt identification and bone marrow transplantation of SCID patients before the onset of severe, life-threatening infections, will result in major improvements in patient outcomes and reduction in the cost from prolonged hospitalisation. The customised genetic testing program will play a key role in identifying the causative gene either through Sanger sequencing of a high probability genetic defect, or through deployment of NGS-based targeted gene panels for SCID.

A national PID service could consist of a hub-and-spoke model. For adult patients, Christchurch would provide the hub for the South Island, while Auckland and Wellington would provide the hubs for the North Island. The unit at Starship would provide the service for the entire country. Regular immunology clinics in regional centres will reduce the need for patients to travel to larger centres.

The model proposed is unique in that both adult and child patients will be treated as part of the integrated national PID service. Such a national PID service may allow combined adult and paediatric immunology clinics in regional centres, which would help seamless transitioning of child patients to adult services, as well as upskilling local physicians on the management and monitoring required for these complex diseases. Currently, a seamless transition between child and adult services is only available in Auckland.

A national PID service, facilitated by the collegiality between adult and paediatric immunologists in New Zealand, will be of great benefit to patients and their families. A schism often exists in other services between provision of care for children as they progress through adolescence to adulthood. In some countries, paediatric immunologists continue care for their patients into late adulthood because of a lack of adult services for patients with PIDs.

Many countries are addressing the challenges posed by rare disorders. Ireland, England, France and the EU as a whole are developing national strategies to deal with patients with rare conditions.[54,55] There have been similar calls for a national service for rare disorders in Australia.[56] A national service for PIDs would support patient-centred management, allowing greater patient autonomy.[57]

We accept there may be some disadvantages for the proposed national PID service. A national PID service will require immunologists having to visit regional centres on a regular basis. Extra immunology positions will be needed for each hub, in Auckland, Wellington, and Christchurch. There are currently several advanced trainees in immunology who could fill these positions over time. A national PID service will also require some investment in infrastructure to co-ordinate joint clinics in regional centres. Practical issues, such as reviewing laboratory results and typing clinic letters, will need to be addressed. These issues are not insurmountable and have been overcome by other national services, such as paediatric rheumatology. It is likely any additional costs for immunology positions and infrastructure will be easily offset by savings from the judicious use of IVIG/SCIG, and reduced hospitalisation costs.

Other models for a nationally co-ordinated service could be considered, where each region with an immunology service remains autonomous. There will be disadvantages with this model as there may be insufficient numbers of immunologists in some areas to provide a visiting service to regional cities. Funding formulas would also need to be carefully considered to ensure regions with fewer immunologists are not disadvantaged. Furthermore, there is only one public hospital paediatric immunology service (based at Starship) for PIDs, which has been providing a de facto national service for PID patients. It will be important for this service to be appropriately resourced.

In the past, there has been resistance to developing national services on account of each DHB having to financially contribute to the program. As we have shown here, smaller DHBs without an immunology service are likely to fiscally benefit most from a national PID service. We are very confident a strong business case could be made for our proposal. We hope the Ministry of Health and the National Health Board will engage with stakeholders, especially the New Zealand Clinical Immunology and Allergy Group (NZCIAG) for productive discussions on this proposal. Patient support groups (IDFNZ and HAE Australasia) will also play an important role in shaping a national PID service. The model proposed here may also be useful for other countries with a centralised government-funded health system.

Competing interests:
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REFERENCES:

1. Al-Herz W, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol, 2014. 5: p. 162.
2. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol, 2009. 145(6): p. 709-27.
3. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol, 1999. 92(1): p. 34-48.
4. Oksenhendler E, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis, 2008. 46(10): p. 1547-54.
5. Quinti I, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol, 2007. 27(3): p. 308-16.
6. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. J Clin Immunol, 2007. 27(5): p. 517-24.
7. Ameratunga R, et al. Fulminant mulch pneumonitis in undiagnosed chronic granulomatous disease: a medical emergency. Clin Pediatr (Phila), 2010. 49(12): p. 1143-6.
8. de Vries E, Driessen G. Educational paper: Primary immunodeficiencies in children: a diagnostic challenge. Eur J Pediatr, 2011. 170(2): p. 169-77.
9. Woon ST, et al. Follicular lymphoma in a X-linked lymphoproliferative syndrome carrier female. Scand J Immunol, 2008. 68(2): p. 153-8.
10. Booth C, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. Blood, 2011. 117(1): p. 53-62.
11. Penno E, Gauld R. How are New Zealand's District Health Boards funded and does it matter if we can't tell? N Z Med J, 2013. 126(1376): p. 71-84.
12. Landon BE, et al. Physician specialization and antiretroviral therapy for HIV. J Gen Intern Med, 2003. 18(4): p. 233-41.
13. Gathmann B, et al. Clinical picture and treatment of 2212 patients

with common variable immunodeficiency. J Allergy Clin Immunol, 2014. 134(1): p. 116-26.

14. Ameratunga R, et al. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. Clin Exp Immunol, 2013. 174(2): p. 203-11.
15. Ameratunga R, et al. New diagnostic criteria for CVID. Expert Rev Clin Immunol, 2014. 10(2): p. 183-6.
16. Ameratuga R, et al. Comparison of diagnostic criteria for Common Variable Immunodeficiency Disorder. Frontiers in Immunology, 2014. 5.
17. Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. Ann Allergy Asthma Immunol, 2007. 99(3): p. 281-3.
18. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. Autoimmun Rev, 2006. 5(2): p. 156-9.
19. Chapel H, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood, 2008. 112(2): p. 277-86.
20. Wehr C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood, 2008. 111(1): p. 77-85.
21. Koopmans W, et al. Variability of memory B cell markers in a cohort of Common Variable Immune Deficiency patients over six months. Scand J Immunol, 2013. 77(6): p. 470-5.
22. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol, 2010. 159(3): p. 344-50.
23. Olinder-Nielsen AM, et al. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. Scand J Infect Dis, 2007. 39(1): p. 44-50.
24. Musher DM, et al. Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. J Infect Dis, 2010. 201(4): p. 516-24.
25. Koopmans W, et al. Clinical variability of family members with the C104R mutation in transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI). J Clin Immunol, 2013. 33(1): p. 68-73.
26. Tiller TL Jr, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. J Pediatr, 1978. 92(3): p. 347-53.
27. Pan-Hammarstrom Q, et al. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet, 2007. 39(4): p. 429-30.
28. Salzer U, et al. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. Blood, 2009. 113(9): p. 1967-76.
29. Popa V. Lymphocytic interstitial pneumonia of common variable immunodeficiency. Ann Allergy, 1988. 60(3): p. 203-6.
30. Ameratunga R, Becroft DM, Hunter W. The simultaneous presentation of sarcoidosis and common variable immune deficiency. Pathology, 2000. 32(4): p. 280-2.
31. Fasano MB, et al. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. Medicine (Baltimore), 1996. 75(5): p. 251-61.
32. Fuss IJ, et al. Nodular Regenerative Hyperplasia in Common Variable Immunodeficiency. J Clin Immunol, 2013. 33(4): p. 748-58.
33. Malamut G, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol, 2008. 48(1): p. 74-82.
34. Luzi G, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. Am J Gastroenterol, 2003. 98(1): p. 118-21.
35. Malamut G, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol, 2010. 105(10): p. 2262-75.
36. Agarwal S, et al. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID)

with intestinal disease. Inflamm Bowel Dis, 2011. 17(1): p. 251-9.

37. Ameratunga R, et al. Profound reversible hypogammaglobulinemia caused by celiac disease in the absence of protein losing enteropathy. Journal of Clinical Immunology, 2015. In press.
38. Ameratunga R, et al. New diagnostic criteria could distinguish common variable immunodeficiency disorder from anticonvulsant-induced hypogammaglobulinemia. Clinical and experimental Neuroimmunology, 2015. 6(1): p. 83-88.
39. Ameratunga RV, Parry S, Kendi C. Hypogammaglobulinemia factitia. Munchausen syndrome presenting as Common Variable Immune Deficiency. Allergy Asthma and Clinical Immunology, 2013. 9(36).
40. Ameratunga R, Sinclair J, Kolbe J. Increased risk of adverse events when changing intravenous immunoglobulin preparations. Clin Exp Immunol, 2004. 136(1): p. 111-3.
41. Smith J, et al. Lamotrigine-induced common variable immune deficiency. Neurology, 2004. 62(5): p. 833-4.
42. Bowen T, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol, 2010. 6(1): p. 24.
43. Shapiro RS, Zacek L. Training hereditary angioedema patients to self-administer intravenous C1 esterase inhibitor concentrate. J Infus Nurs, 2014. 37(4): p. 284-90.
44. Betschel S, et al. Canadian hereditary angioedema guideline. Allergy Asthma Clin Immunol, 2014. 10(1): p. 50.
45. Farkas H, et al. Home treatment of attacks with conestat alfa in hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Proc, 2014. 35(3): p. 255-9.
46. Ameratunga R, et al. The clinical utility of molecular diagnostic testing for primary immune deficiency disorders: a case based review. Allergy Asthma Clin Immunol, 2010. 6(1): p. 12.
47. Ameratunga R, et al. Primary immune deficiency disorders in the South Pacific: the clinical utility of a customized genetic testing program in New Zealand. Ann N Y Acad Sci, 2011. 1238: p. 53-64.
48. Ameratunga R, Woon ST. Customised molecular diagnosis of primary immune deficiency disorders in New Zealand: an efficient strategy for a small developed country. N Z Med J, 2009. 122(1304): p. 46-53.
49. Ameratunga R, et al. Molecular pathology of the X-linked hyper-immunoglobulin M syndrome: detection of wild-type transcripts in a patient with a complex splicing defect of the CD40 ligand. Clin Diagn Lab Immunol, 1996. 3(6): p. 722-6.
50. Fliegauf M, et al. Haploinsufficiency of the NF-κB1 Subunit p50 in Common Variable Immunodeficiency. The American Journal of Human Genetics, 2015. 97(3): p. 389-403.
51. Ameratunga R, et al. Application of diagnostic and treatment criteria for common variable immunodeficiency disorder. Expert Rev Clin Immunol, 2015. (in press).
52. Raje N, et al. Utility of next generation sequencing in clinical primary immunodeficiencies. Curr Allergy Asthma Rep, 2014. 14(10): p. 468.
53. Gahl WA, et al. The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. Genetics in medicine : official journal of the American College of Medical Genetics, 2012. 14(1): p. 51-9.
54. Guillevin L. [The national plan for orphan rare diseases: nearly 10 years on]. Revue neurologique, 2013. 169 Suppl 1: p. S9-11.
55. Taruscio D, Vittozzi L, Stefanov R. National plans and strategies on rare diseases in Europe. Advances in experimental medicine and biology, 2010. 686: p. 475-91.
56. Jaffe A, et al. Call for a national plan for rare diseases. Journal of paediatrics and child health, 2010. 46(1-2): p. 2-4.
57. Burton J, Murphy E, Riley P. Primary immunodeficiency disease: a model for case management of chronic diseases. Professional case management, 2010. 15(1): p. 5-10, 12-4; quiz 15-6.