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Utility of Expanded Genetic Analysis for Pediatric Patients with Primary Immunodeficiency

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ABSTRACT

Background: Given the heterogenicity among primary immune deficiency (PID) or inborn errors of immunity presentations, genetic testing can aid in diagnosis. Despite the convenience of genetic testing, numerous challenges arise, including accessibility and cost.
Aims: Our goal was to determine if a gene panel approach was sufficient in identifying PID or if expanded testing would be more beneficial.
Methods: A retrospective chart review analyzed the diagnostic yield for all patients with suspected PID that underwent PID panel testing at our hospital. Subsequently, from January 2021 to August 2024 caregivers of patients with a negative or non-diagnostic PID panel result were consented for additional exome analysis. Expanded analysis was performed via genotypic-based and phenotypic-driven analysis derived from Human Phenotype Ontology terms from chart notes. Variants of potential clinical interest were identified utilizing American College of Medical Genetics and Genomics recommendations for sequence variant interpretation. Variants of interest were cross-referenced to patient phenotype.
Results: Of the 174 panels run, there was a positive diagnostic yield of 19%. Twelve patients had expanded analysis completed with mean age of symptom presentation of 4.3 years. Expanded analysis identified numerous additional variant of uncertain significance as well as 1 new pathogenic variant.
Conclusion: This analysis resulted in a minimal increase in diagnostic yield compared to panel testing. Although only 1 new pathogenic variant consistent with the patient's phenotype was identified; the increase in variants of interest from the expanded analysis supports the value of ongoing genomic reanalysis. Given the comparable diagnostic yield, PID panels remain a cost-effective approach at this time.
Keywords: Primary Immunodeficiency, Inborn Errors of Immunity, Whole Exome Genetic Testing, Genetic

Abbreviations/Acronyms:

WES - whole exome sequencing
IEI - inborn errors of immunity
SCID - severe combined immunodeficiency
WGS - whole genome sequencing
PID - primary immune deficiency
ACMG - American College of Medical Genetics and Genomics
VUS - variants of uncertain significance
PFAPA - periodic fever, aphthous stomatitis pharyngitis and adenitis
CVID - common variable immunodeficiency
CGD - chronic granulomatous disease
ITP - immune thrombocytopenic purpura
IUIS - International Union of Immunological Societies

Introduction

Primary immune deficiency (PID) or inborn errors of immunity (IEI), the diverse group of disorders resulting from defects in the immune system function or development[1,2], should be suspected in patients with recurrent, severe or unusual infections, failure to thrive, a poor response to prolonged antimicrobials or autoimmune/autoinflammatory diseases.[3-6] Initial lab testing for PID is guided by specific history of recurrent infections and physical exam findings.[3] If initial lab testing is inconclusive, targeted genetic testing approaches can aid in a diagnosis.

Diagnostic yield rates of PID-related panel testing vary significantly in the literature with yields ranging between 15-46%.[7] Genetic analysis results demonstrate substantial variability, which is influenced by multiple technical, biological, and population-related factors. As approximately 80% of genome-wide association study participants are of European descent, population diversity created a significant bias in variant classification for other populations.[8] With the perpetually changing nature of the International Union of Immunological Societies (IUIS) Immunology Databases[9], different labs can produce different results despite analyzing for PID. Furthermore, temporal variability occurs as scientific knowledge continually evolves.

Although inborn errors of metabolism are routinely screened for in newborn screens, severe combined immunodeficiency (SCID) is the only PID that is currently on the newborn screen. Beyond SCID, expanded genetic analysis is available for patients with concern for PID that were not detected on the newborn screen. Given the heterogenicity among PID presentations, genetic testing can aid in diagnosis, and if results confirm a diagnosis this can impact management.[3] Current genetic testing workflows revolve around panels which target overlapping phenotypes that are suspicious for a genetic cause of PID by utilizing a predefined gene list. Advantages of genetic panels provide a broad evaluation of probable contributory genes and limit unwanted secondary findings unrelated to the patient's phenotype. Although genetic panels can be very useful in diagnosing PID, they are not all-encompassing and lack the breadth of an expanded genetic analysis, such as whole exome sequencing (WES) or whole genome sequencing (WGS). Despite the convenience of genetic testing, numerous challenges arise, including accessibility and cost.[10] As such, genetic testing is typically performed in a stepwise manner.

At our institution, the standard work up for a patient with suspected PID is a PID panel that tests for approximately 300-400 genes associated with immunodeficiency; smaller panels are also available for indications such as periodic fever. Although the panel is comprehensive, continuing genomic research begets an expanding source of data, particularly in number of new additional genes associated with immunodeficiency. Our goal was to determine if our current diagnostic practices of a PID-related panel were sufficient in identifying PID or if expanded testing, via a medical exome, would be more beneficial.

Methods

To determine the diagnostic yield of PID panels done for our hospital's patients, a retrospective analysis was done of 174 patient charts. This analysis evaluated each patient who had a PID-related panel done through our molecular laboratory or outside laboratories since 2018. Each genetic testing panel report included indications for testing, number of genes evaluated, a list of each variant for that patient and their classifications. Positive diagnosis was defined as written evidence in the patient's charts of an official diagnosis or symptoms that aligned with the identified genetic variant classified as "Pathogenic or Likely Pathogenic". The genetic variants were classified in accordance with the 2015 American College of Medical Genetics and Genomics Recommendations (ACMG)[11] as Pathogenic, Likely Pathogenic or Variant of Unknown Significance (VUS) and both in-house and commercial panels received gene panel content updates derived from IUIS Immunology Databases.[9] All results from in-house genetic testing at a classification of pathogenic or likely pathogenic received Sanger sequencing as an orthogonal method of result confirmation, a practice commonly employed by commercial laboratories as well. Variants classified as Likely Benign or Benign were not included on the reviewed reports. An additional category of "Inconclusive" was created by the authors to identify patients who were heterozygous carriers of a pathogenic or likely pathogenic variant in an autosomal recessive (or X-linked for females) condition and no other causative variants were identified to complete the inheritance pattern. Of note, reports by some commercial laboratories included an additional category of "Increased Risk". Increased Risk variants were defined as increasing a patient's risk for certain diseases but do not necessarily cause disease in a traditional Mendelian fashion. Diagnostic yield was assessed by review of clinician notes and patient communications where diagnosis was discussed in conjunction with the genetic variant found in the PID panel. Patient charts were reviewed by a medical student, resident and attending for final diagnostic yield determination. Statistical analysis was performed to report counts and percentage of positive and negative results as a sum of the total number of patients. Graphs were created using Microsoft Excel software.

Patients with a non-diagnostic genetic evaluation, then underwent further expanded genetic testing in an attempt to increase diagnostic yield. Patients were identified by their primary immunologist or rheumatologist for expanded genetic analysis based on patient's high phenotypic concern for an inborn error of immunity. This included recurrent hospitalizations due to infections such as sinopulmonary infections and bacteremia, cytopenias (such as immune mediated thrombocytopenia), and periodic fevers. No specific lab values were used for identification. From January 2021 to August 2024 caregivers of patients at our institution with a negative or non-diagnostic PID-related panel result were consented for additional analysis of the medical exome, which encompasses approximately 4600 genes known to be associated with human disease. Expanded analysis was performed by bioinformatically unmasking existing sequencing data from the initial panel. Two individual researchers utilized a parallel genotype and phenotype driven analysis. Phenotype driven analysis was compiled via chart review of Human Phenotype Ontology terms. Genotype driven analysis was performed utilizing data points derived from ACMG[11] recommendations for sequence variant interpretation (e.g. rare or absent from controls, predicted severe effect on protein, presence of variant in published literature). Variants of interest were then cross-referenced to the patient phenotype for a potential match and etiology of disease. The study was reviewed by our institution's Institutional Review Board and approved (IRB 2021-4065).

Results

1. OVERALL DIAGNOSTIC YIELD

At our institution, there have been 96 PID-related sequencing panels performed in house to date. Within the hospital, genetic testing can also be sent out to other clinical laboratories; in total, since 2018, 174 PID-related panels have been performed inclusive of in-house and outside clinical laboratories. Of the 174 immunodeficiency panels run at our hospital during the study, there was a positive diagnostic yield of 19% (Table 1). There were 96 panels performed by our institution's in-house laboratory since 2018 with a diagnostic yield of 17.7%. Seventy-eight panels were performed by commercial laboratories with a diagnostic yield of 20.5%. A positive diagnosis was clinically defined as written evidence in a patient's chart of an official diagnosis or symptoms that highly correlated with the genetic variant with suspicion of pathogenicity.

Table 1: Diagnostic Yield for Immunodeficiency Panels at Our Institution

Our Institution's Laboratories Panels		**% of Total**
Positive	17	17.7%
Negative	79	82.3%
Commercial Panels		
Positive	16	20.5%
Negative	62	79.5%
All Panels		
Positive	33	19.0%
Negative	141	81.0%

Of the 17 panels that resulted in a positive diagnostic yield for patients, 11 of the variants were Pathogenic, 4 were Likely Pathogenic and 2 were classified as a VUS. An example of a patient classified as a positive diagnosis with a VUS variant was a patient with periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) with a single VUS in MEFV. Although MEFV variants are usually more correlated to Familial Mediterranean Fever, there have been cases of atypical PFAPA and MEFV variants.[12] The patient presented with young onset periodic fevers with a lack of periodicity and good responsiveness to oral steroids. Although PFAPA is a diagnosis of exclusion, the patient's responsiveness to oral steroids and MEFV variant led to the diagnosis. The commercial panels that resulted in a positive diagnostic yield included 9 Pathogenic variants, 3 Pathogenic carriers, 2 Likely Pathogenic variant and 2 Increased Risk genes (Table 2 and 3).

Table 2: Our Institution's In-House Variant Classification

Report Classification	**Number of Patients**	**% of Total**
Pathogenic	12	12.5
Likely Pathogenic	4	4.2
VUS	70	72.9
Inconclusive	10	10.4

Table 3: Commercial Panel Variant Classifications

Report Classification	**Number of Patients**	**% of Total**
Pathogenic	8	10.3
Pathogenic Carrier	15	19.2
Likely Pathogenic	1	1.3
Likely Pathogenic Carrier	1	1.3
Increased Risk	4	5.1
VUS	37	47.4
Negative	9	11.5
Multiple Classifications	3	3.8

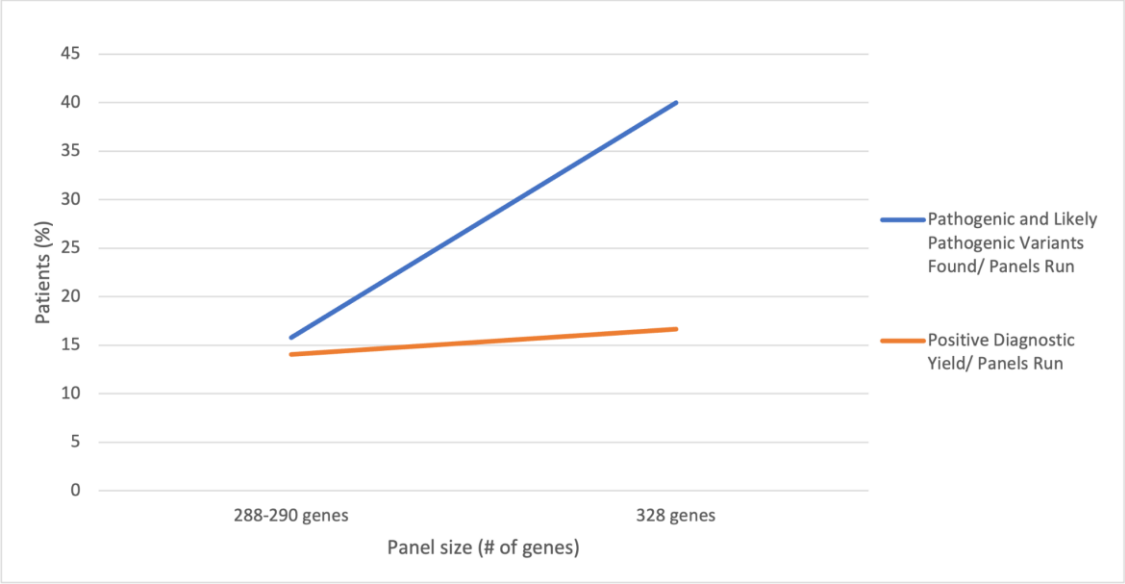
The primary indication for testing, as reported by the ordering provider, was concern for immunodeficiency (Table 4). Of the number tested, 12 patients were filtered into expanded genetic protocol.

Table 4: Most Common Clinical Indications for Testing in In-House Panels (>5 patients)

Indications	Number of Patients
Immunodeficiency (including CVID, SCID, and selective hypogammaglobulinemia)	23
Recurrent/Severe Infections	18
Thrombocytopenia	16
Neutropenia	13
Anemia (general, not including AIHA)	13
Autoimmune Disease	12
Lymphadenopathy	8
Autoimmune Hemolytic Anemia (including evidence of hemolysis and positive direct antiglobulin test)	7
Respiratory/Hypoxemia/Lung Disease	7
Evan's Syndrome	6

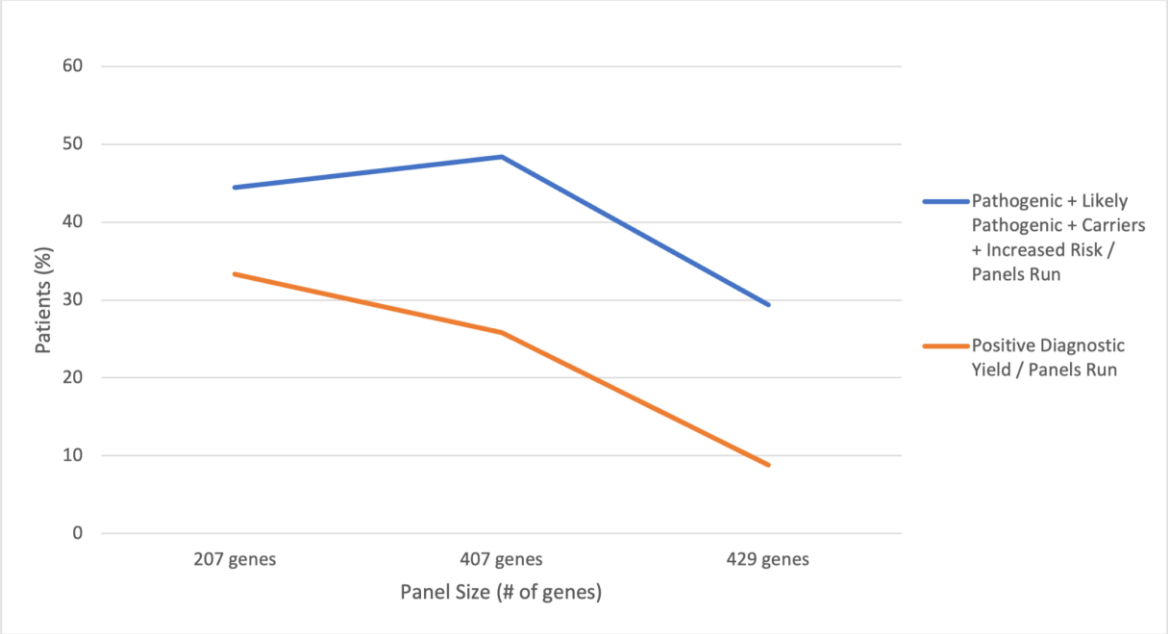
The number of genes on PID-related panels at our hospital and commercial laboratories have increased as knowledge surrounding gene-disease phenotypes continues to improve. In the time period of this study the comprehensive PID in-house panel has expanded from 288 genes to 328 genes. In our data, there were 57 patients who had panels with 288 genes and 30 patients with panels of 328 genes. The diagnostic yield increased from 14% to 17% with an additional 40 genes added (Figure 1).

Figure 1: Our Institution's Laboratory Pathogenic/Likely Pathogenic Variants and Diagnostic Yield for Different Panel Sizes



For the commercial panel, there was an expansion from 207 genes to 407 genes and the panel now tests for 429 genes (Figure 2). There were 9 patients with panels of 207 genes, 31 patients with panels of 407 genes and 24 patients with panels of 429 genes. The diagnostic yield for these three panel sizes is 33%, 26% and 9%, respectively. Given the changes in number of genes tested in both the commercial and in-house panels, our analysis for panels with gene counts that did not fit into the panel size categories listed above were excluded. Thus, 9 panels were omitted from in the in-house analysis and 14 from the commercial laboratories.

Figure 2: Commercial Panel Pathogenic + Likely Pathogenic + Carriers + Increased Risk Variants and Diagnostic Yield for Different Panel Sizes



2. EXPANDED ANALYSIS

Twelve patients, 8 females and 4 males, were consented for expanded analysis, with age of symptom presentation ranging from 7 months to 12 years old (mean 4.3 years). One patient had a positive initial PID panel with a disease causing variant in the TNFRSF13B gene, associated with common variable immunodeficiency (CVID), but this was not found to fully explain the patient's phenotype. Of the remaining 11 patients, one had a negative initial PID panel and 10 were inconclusive with numerous variants of uncertain significance (VUS) that did not match the clinical phenotype of the patients (Table 5).

Table 5. Expanded Analysis Sample Demographics and PID Results

	Patients (n=12)
Male	4
Female	8
Mean age of symptom onset	4.3 years
Initial PID Panel Pathogenic Variants	1
Initial PID Panel VUS	37
Variants identified in expanded analysis matching patient's phenotype	1

After expanded genetic analysis, all 37 of the previously reported variants that were from the initial PID panel were identified. In addition, expanded analysis identified an additional 81 variants of potential interest. After review, 5 variants were flagged for further evaluation given a potential match to patient phenotype or suspicion of disease impact (Table 6). The variants identified were heterozygous and associated with various immune dysregulation phenotypes. Expanded analysis for 1 patient identified a potentially disease causing variants in MECOM.

Table 6. Variants of Clinical Interest Identified via Expanded Analysis

Gene	**Variant Genomic Coordinate**	**Variant Change**	**Zygosity**	**Inheritance**	**Mutation Type**	**Variant Phenotype**	**Variant Considered Clinically Significant**
MECOM	Chr3:169116164	AG>A c.1143del p.Phe382Leufs*54	Heterozygous	AD	Stop gained (Deletion)	Radioulnar Synostosis with Amegakaryocytic Thrombocytopenia	Yes
NCF1	chr7:74783529	G → A c.579G>A p.Trp193*	Heterozygous	AR	Stop Gained	Chronic Granulomatous disease	No
TNFRSF1A	Chr12:6333477	C>T c.362G>A p.Arg121Gln	Heterozygous	AD	Missense	Familial autosomal dominant Periodic fever, Bechet syndrome	No

Gene	Variant Genomic Coordinate	Variant Change	Zygosity	Inheritance	Mutation Type	Variant Phenotype	Variant Considered Clinically Significant
ITGB3	Chr17:47299424	G>A c.1807G>A p.Gly603Ser	Heterozygous	AR	Missense	Glanzmann Thrombasthenia	No
UNG	Chr12:109103431	A>G c.623-2A>G	Heterozygous	AR	Splice Acceptor	Immunodeficiency with hyper-IgM	No

AD: autosomal dominant, AR: autosomal recessive.

The variant p.Phe382Leufs*54 in the MECOM gene was identified and classified as a likely pathogenic variant on expanded analysis of the initial PID panel for a patient with recurrent sinonasal infections, frequently preceded by profuse bouts of epistaxis, and recent joint injuries suspected to be secondary to joint hypermobility. Disease causing variants in this gene are associated with Radioulnar Synostosis with Amegakaryocytic Thrombocytopenia. This patient has not exhibited bony abnormalities, but does have a prior diagnosis of neonatal thrombocytopenia, with chronic thrombocytopenia and absolute lymphopenia into adolescence. Upon further genetic sequencing completed for this patient's parents, it was found that the patient's variant was not inherited from either parent representing a de novo finding. While de novo variants in the MECOM gene have been identified, this specific variant has not been reported in the literature. Prior reviews of the literature detail MECOM-associated deletions to be around 8.5% of all MECOM variants, supporting loss of function as a mechanism of disease and an elevated suspicion of this patient's variant.[13] However, three patients have been identified with heterozygous missense mutations in MECOM at three different loci who developed bony and bone marrow irregularities prior to age one year, which differs from our patient's presentation.[14-16]

The variant p.Trp193* in the NCF1 gene was identified as a potential variant for a patient that presented with recurrent acute otitis media, recurrent sinusitis, chronic spontaneous urticaria, clostridium difficile, and helicobacter pylori. Although the patient does not match the classic presentation of an NCF1 mutation causing chronic granulomatous disease (CGD), such as granuloma formation, inflammatory bowel disease, granulomatous colitis, and abscesses; the patient presented at 22 months old and could continue to develop further symptoms. Initial testing for CGD with neutrophil-function testing was unremarkable, but flow cytometry dihydrorhodamine neutrophil burst assays can be fraught with false negatives.[17] Given the autosomal recessive inheritance pattern of this gene, a microarray to examine for potential copy number variants was sent and is pending; no other sequence variants of interest in this gene were identified in the patient.

The variant p.Arg121Gln in the TNFRSF1A gene was classified as a VUS on the initial PID panel and reidentified on the expanded analysis for one patient. This variant is a well-known variant that has been identified in several individuals with periodic fever, such as autosomal dominant periodic fever syndrome, in the literature, but is consistently reported as mild with data suggesting a low penetrance variable mutation. The inconsistent nature of this variant is challenging for classification as the ACMG guidelines do not account for variants best suited as non-Mendelian risk alleles.[18-22] The patient had recurrent fevers and poor growth necessitating a referral to a gastroenterologist and further laboratory work-up. The labs were notable only for severe neutropenia that resolved over time. Otherwise, work up at this time is unremarkable. Given the incomplete phenotypic match and variant change, this gene was identified as interesting but not a potential variant for the specific patient.

The variant p.Gly603Ser in the ITGB3 gene was identified on expanded analysis in a patient presenting with chronic immune thrombocytopenic purpura (ITP) at 12 years old, requiring IVIG, prednisone, and subsequently Romiplostim. The initial PID panel identified p.Arg121Gln in the TNFRSF13B gene as a likely pathogenic variant, which is associated with CVID. Although TNFRSF13B variants have a well-known association with cytopenias[23], the patient's lab results and clinical history did not match CVID, so the expanded genetic analysis was performed which identified the variant in ITGB3. The ITGB3 gene encodes glycoprotein IIIa, and variants in this gene are associated with Glanzmann Thrombasthenia, which is not consistent with ITP. Moreover, our patient had thrombocytopenia on their labs, which would not be seen in Glanzmann Thrombasthenia.[24]

The variant c.623-2A>G in the UNG gene was identified in the initial PID panel and re-reviewed in expanded analysis in a patient presenting with recurrent acute otitis media developed pseudomonas bacteremia, multiple pontine brain abscesses, and ecthyma gangrenosum at 5 years old. This variant affects the canonical splice site (c.623-2A>G); disease causing variants in this gene are associated with Hyper-IgM Immunodeficiency 5 (HIGM5), where patients have susceptibility to recurrent sinopulmonary infections predominantly with encapsulated bacteria. Interestingly, our patient's primary organisms cultured continued to be pseudomonas aeruginosa, an encapsulated, gram-negative rod. A study by Nilsen et al. of UNG-deficient mice showed the role of the enzyme on DNA replication, which was difficult to interpret the mutation as these mice did not exhibit a significantly increased spontaneous mutation frequent.[25] A subset of 3 patients with HIGM5 caused by a mutation in UNG studied by Imai et al. had susceptibility to bacterial infections and lymphoid hyperplasia with labs showing elevated IgM and decreased IgA and IgG[26], which does not match our patient's labs at this time.

Discussion

The diagnostic yield of immunodeficiency related panels run at our institution since 2018 was 19%. Expanded analysis was able to identify all previously reported PID panel variants and several interesting variants were identified to provoke additional clinical review. However, despite expanded analysis for 4,600 genes, only one additional clinically significant variant was identified in the expanded genetic analysis. Although the overall yield was low, our findings suggest expanded genetic analysis remains beneficial in certain cases.

The positive diagnostic yield of 19% from PID-related panels run at our institution is similar to other institutions with a range of 15-46% for mixed PID panels.[7] It is worth noting that our commercial and in-house panels increased in number of genes tested over time and were not identical so generalizability is limited. Given the intermediate diagnostic yield both at our institution and the field overall, it is clear that genetic testing does not always yield a molecular diagnosis for these patients. Furthermore, patients who are identified to harbor a variant classified as Pathogenic or Likely Pathogenic, may not always correlate with a positive diagnosis at the clinical phenotype level. In our study, one patient had a variant consistent with their phenotype, though the variants were classified at only a VUS level, which highlights the need for clinical correlation for phenotype matching. Thus, providers should use the genetic report as a tool in conjunction with patient symptoms and clinical tests as part of a comprehensive workup. Expanded testing can provide valuable clinical insights, but it also generates more VUS results, requiring significant time to evaluate their clinical relevance.

Since 2018, the internal PID panel at our molecular laboratory has expanded from 288 genes to 328 genes resulting in an increased diagnostic yield of 14% to 17% with an additional 40 genes added (Figure 1). Commercial laboratories have expanded their PID panel three times from 207 to 407 and now at 428 genes. The diagnostic yield in our study for these three panel sizes is 33%, 26% and 9%, respectively (Figure 2). Counterintuitively, this data shows that with a larger number of genes tested through commercial panels, there is a decrease in the diagnostic yield. These conflicting results demonstrate that more genes in the panel does not necessarily correlate to a larger diagnostic yield. Consistent with our data, a publication by Arts et al. from 2019 used WES as a first-tier genetic test and identified a diagnosis in 28% of patients, largely consistent with the documented diagnostic yield rate of panel-based tested.[27] There were limitations to these results including an unequal number of patients in each group of panel sizes, small sample sizes, and a spectrum of patient presentations. Moreover, as PID panel testing could be ordered by various providers throughout our large tertiary care hospital system, such as immunologists, rheumatologists and intensivists, ordering of WES is currently limited. Furthermore, commercial panels were utilized for logistical or cost issues on a patient-by-patient basis. As such the study contains selection bias, namely channeling bias. Despite these limitations, this may further support that expanding analysis does not always yield more positive results.

There remains a need to balance between the utility of WES/WGS and PID panels. Although panel based tests frequently alter the number of genes tested with the ability to test for more genes; the cost-benefit analysis for genetic testing must continually be analyzed. National and international consortiums such as IUIS that regularly review genes to be included on specific genetic panels can aid in overall diagnostic yield[9] and harmonization of test offerings. Given the large number of IEIs and a spectrum of logistical barriers to WES/WGS, the most efficient approach in terms of cost and time would be to start with personalized genetic panels based on clinical suspicion and expanding as necessary. It is acknowledged that large scale testing of WES/WGS ostensibly removes this burden but carry their own limitations including cost, insurance coverage, turnaround time and provider-patient considerations such as identification of issues of paternity, incongruent sex assigned at birth findings, and identification of genetic predispositions unrelated to the patient indication among other possibilities.

In either methodology of genetic testing, intermittent reanalysis should be considered in patients with non-diagnostic results given the expanding knowledge base within this subspecialty. While this requires further resource investment by clinicians, it could yield previously unknown and valuable diagnostic information. Although a variant may initially present as a VUS, interesting variants could provide further information and flags as these patients continue to grow older and further define their disease presentation.

Conclusion

Genetic testing is complicated and time consuming, requiring extensive examination and recognition of the nuances associated with the testing process. Our study demonstrates that expanding genetic analysis may provide further clinical answers for some patients but could also increase the number of genes unrelated to a patient's clinical phenotype. In a large tertiary-care hospital system, strategic testing is important to balance cost, efficiency, and diagnostic yield. Based on our study, for hospital systems with particularly limited resources, expertise and accessibility to genetic testing, it could be reasonable at this juncture to solely perform a dedicated PID panel for patients with an appropriate indication given the consistent diagnostic yield. Although WES/WGS carry many benefits and may have a higher overall yield, targeted genetic panel tests remain a cost-effective and efficient method for PID diagnosis and could be a sufficient means for genetic analysis. As the cost and burden of ordering large scale genetic testing becomes more accessible to both providers and patients, this may be the avenue of the future for genetic testing for PID.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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