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GENETIC TESTING IS INDICATED IN THE ROUTINE EVALUATION OF ADULT PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY - PRO

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Genetic Testing in the Routine Evaluation of Adult Patients with CVID

HOW DOES THIS CHANGE MANAGEMENT?

OUTLINE

- Brief **overview** of common variable immunodeficiency (CVID)
- Review **diagnostic criteria** for CVID and **complications** of CVID
- Review **current genetic landscape** in CVID
- Discuss **utility** and **financial implications** of genetic testing

COMMON VARIABLE IMMUNODEFICIENCY (CVID)

- Severe form of a primary antibody deficiency with heterogenous phenotypes and etiologies
- Onset of symptoms can occur from early childhood to the eighth decade or later (Gathmann et al.), but most often diagnosed in third decade of life or later
- Current estimates suggest a prevalence of 1:25,000 Caucasian individuals (Bonilla et al.)
- Usually significant delay between onset of symptoms and diagnosis

CASE

- HPI: **64yo Caucasian male referred for hypogammaglobulinemia**
- Pertinent medical history
  - Age 40 – post-viral ITP, resolved after high-dose IVIG
  - Age 43 – Hashimoto's thyroiditis
  - Age 51 – developed lymphadenopathy and ultimately was diagnosed with Burkitt's lymphoma
  - Age 52 – recurrence of lymphadenopathy, found to have granulomatous LN
    - Diagnosed with CVID and started on IVIG q12 weeks

Adapted from Dr. Williams, AAIFNC Annual Meeting 2025

CASE

- HPI: **64yo Caucasian male referred for hypogammaglobulinemia**
- Pertinent lab evaluation (done 12 weeks after IVIG)
  - WBC 5.5k, Hgb 13.6, Plt 164, ANC 2380, ALC 2440
  - IgG 814, **IgA 36**, IgM 108, IgE <25
  - IgG Diphtheria 0.4, Tetanus 2.4, S. pneumo 18/23 protective
  - Normal CD3, CD4, CD8, CD19 (281), NK cells
- Close observation

Adapted from Dr. Williams, AAIFNC Annual Meeting 2025

CASE

- A year goes by and he remains clinically well, but his IgG is trending down
  - 793 -> 574 -> 521 -> 381 -> 289 -> 367
  - Now with poor specific antibody production
  - No infections
- Continued observation
- Develops axillary lymphadenopathy
  - Florid follicular hyperplasia with + EBER
  - Flow not consistent with malignancy
  - PET scan with diffuse hypermetabolic activity within the enlarged spleen, scattered hypermetabolic LNs in the neck, chest, and abdomen – some improved, some increased

Adapted from Dr. Williams, AAIFNC Annual Meeting 2025

COMMON VARIABLE IMMUNODEFICIENCY (CVID)

- An "umbrella" diagnosis
- No single clinical feature or laboratory test pathognomonic for CVID
- Identification of CVID therefore relies on diagnostic criteria

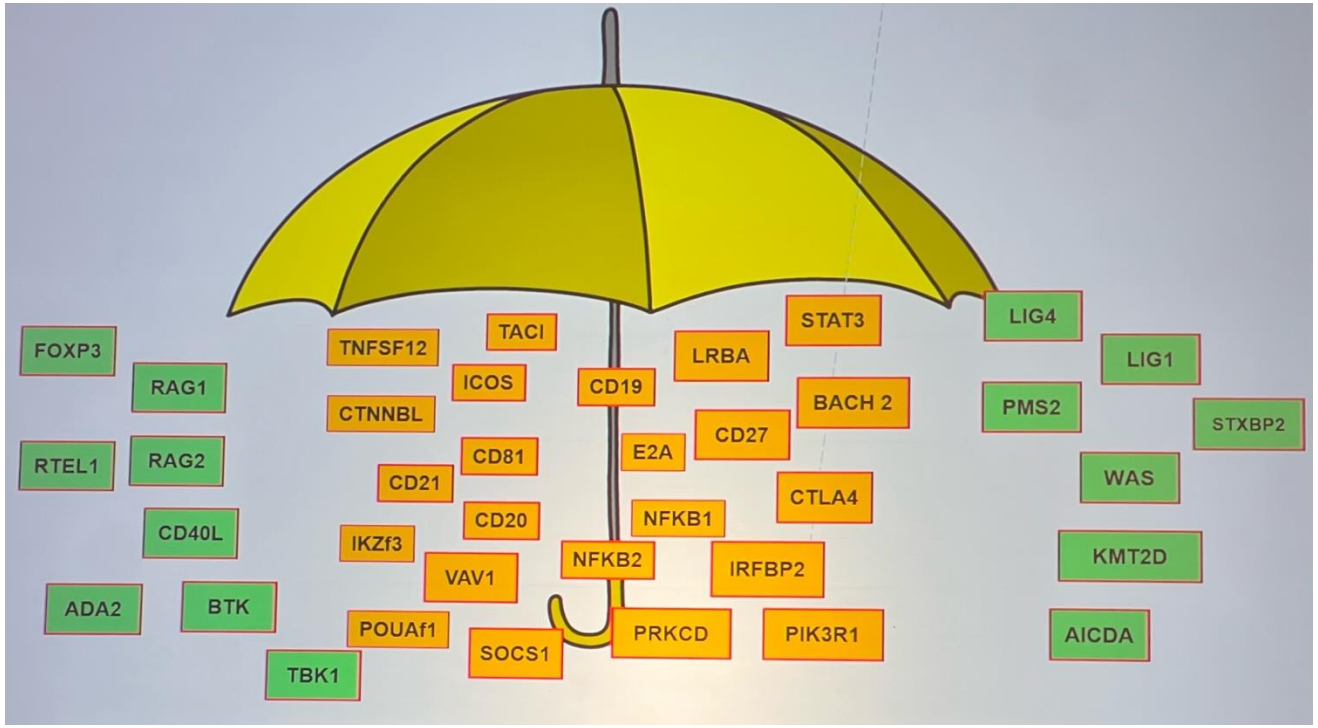
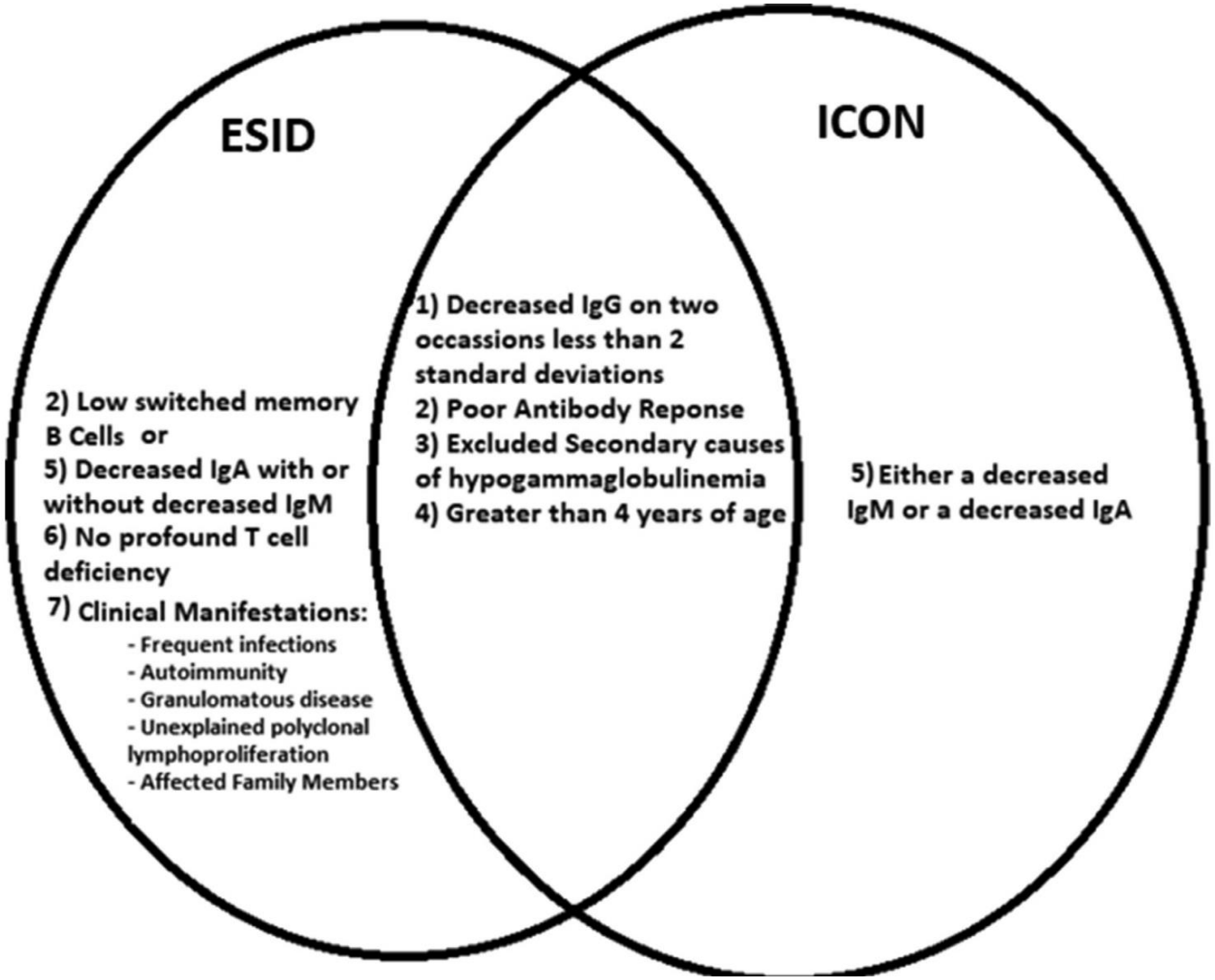


Image courtesy of Dr. Cunningham-Rundles, CIS Annual Meeting 2025



Lee et. al

DIAGNOSTIC CRITERIA

COMMON VARIABLE IMMUNODEFICIENCY (CVID)

- Majority of patients with CVID present with recurrent and severe infections, although many have non-infectious manifestations
- Untreated, patients are predisposed to chronic suppuration of the respiratory tract, often resulting in chronic sinus disease and bronchiectasis
- Approximately 25% of CVID patients have autoimmune or inflammatory sequelae (Ameratunga et al.)
- Increased risk of malignancy (Kralickova et al.)

INFECTIOUS MANIFESTATIONS

- **Recurrent bacterial sinopulmonary infections**
- Recurrent, severe or deep seated pyogenic bacterial infections
- Recurrent fungal infections
- Opportunistic and live viral vaccine-related infections
- **Diffuse cutaneous viral infections**
- Susceptibility to unusual or atypical pathogens
- HSV encephalitis
- Recurrent Neisseria meningitis
- **Persistent CMV or EBV viremia**

NON-INFECTIOUS MANIFESTATIONS

- Occur in >67% of CVID patients (Ho et al.)
- Often the first and/or only presenting clinical symptom
- Typically not improved by immunoglobulin replacement therapy
- For patients on immunoglobulin replacement therapy, **non-infectious manifestations are the leading cause of morbidity and mortality in CVID**

NON-INFECTIOUS MANIFESTATIONS

- Autoimmunity (e.g. cytopenias, multiple forms of organ-specific autoimmunity)
- Autoinflammation (e.g. recurrent fevers +/- rashes, arthralgias, abdominal pain, oral ulcers)
- Lymphoproliferation (e.g. lymphadenopathy, hepatomegaly, splenomegaly)
- Inflammatory bowel disease
- Interstitial lung disease or non-CF related bronchiectasis
- Malignancy (e.g. leukemias, lymphomas)

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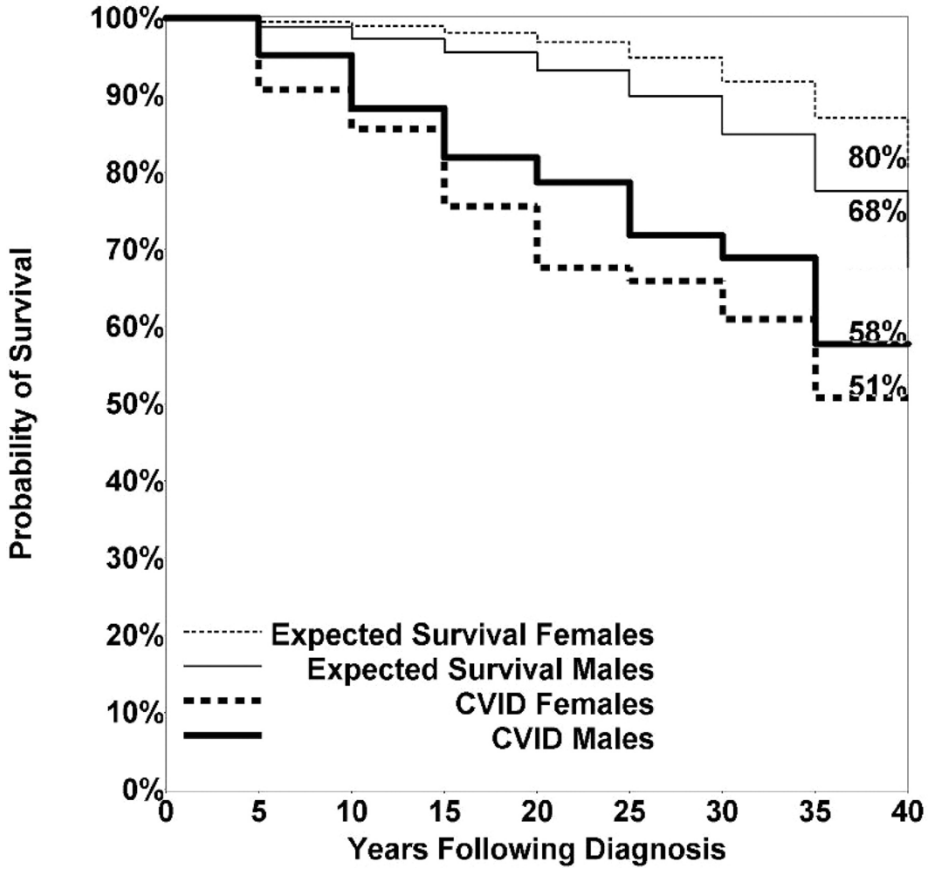
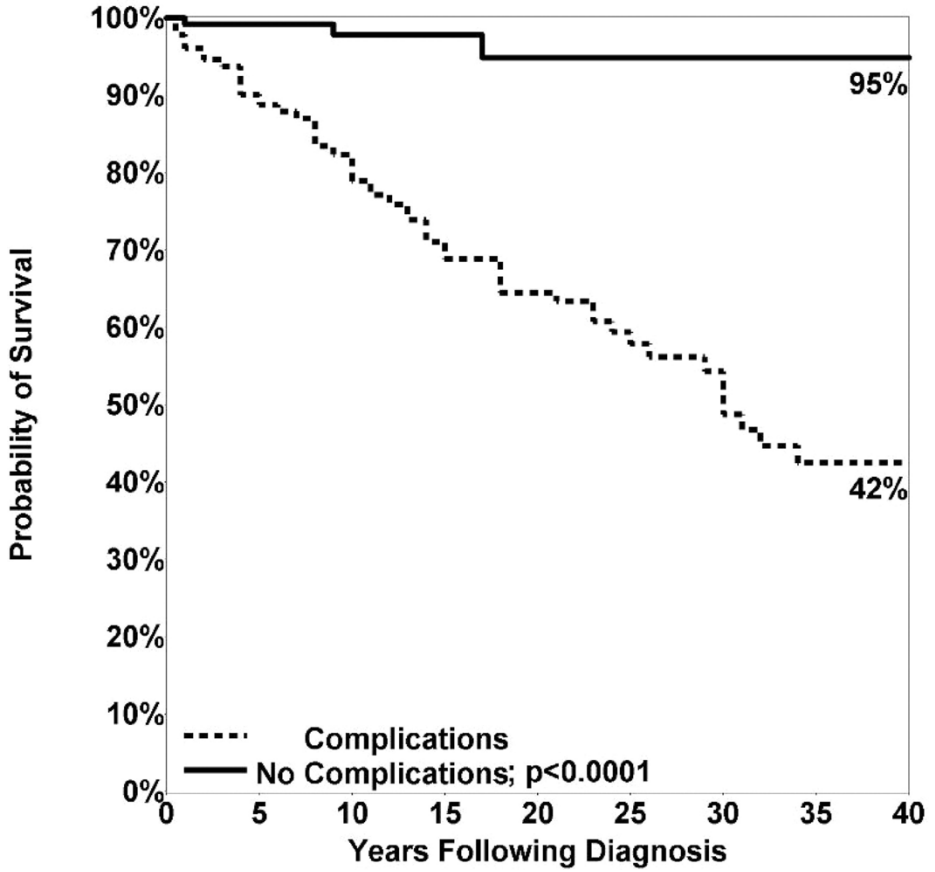




Resnick et al.

CVID DECREASES SURVIVAL

MANAGEMENT OF CVID

- **64yo male with history of Burkitt's lymphoma s/p rituximab, now with CVID and benign lymphadenopathy**
- Treatment options
  - Immunoglobulin replacement therapy
  - Prophylactic antibiotics

CAN WE DO MORE FOR THIS PATIENT?

MOLECULAR GENETIC TESTING FOR CLINICAL DECISION-MAKING

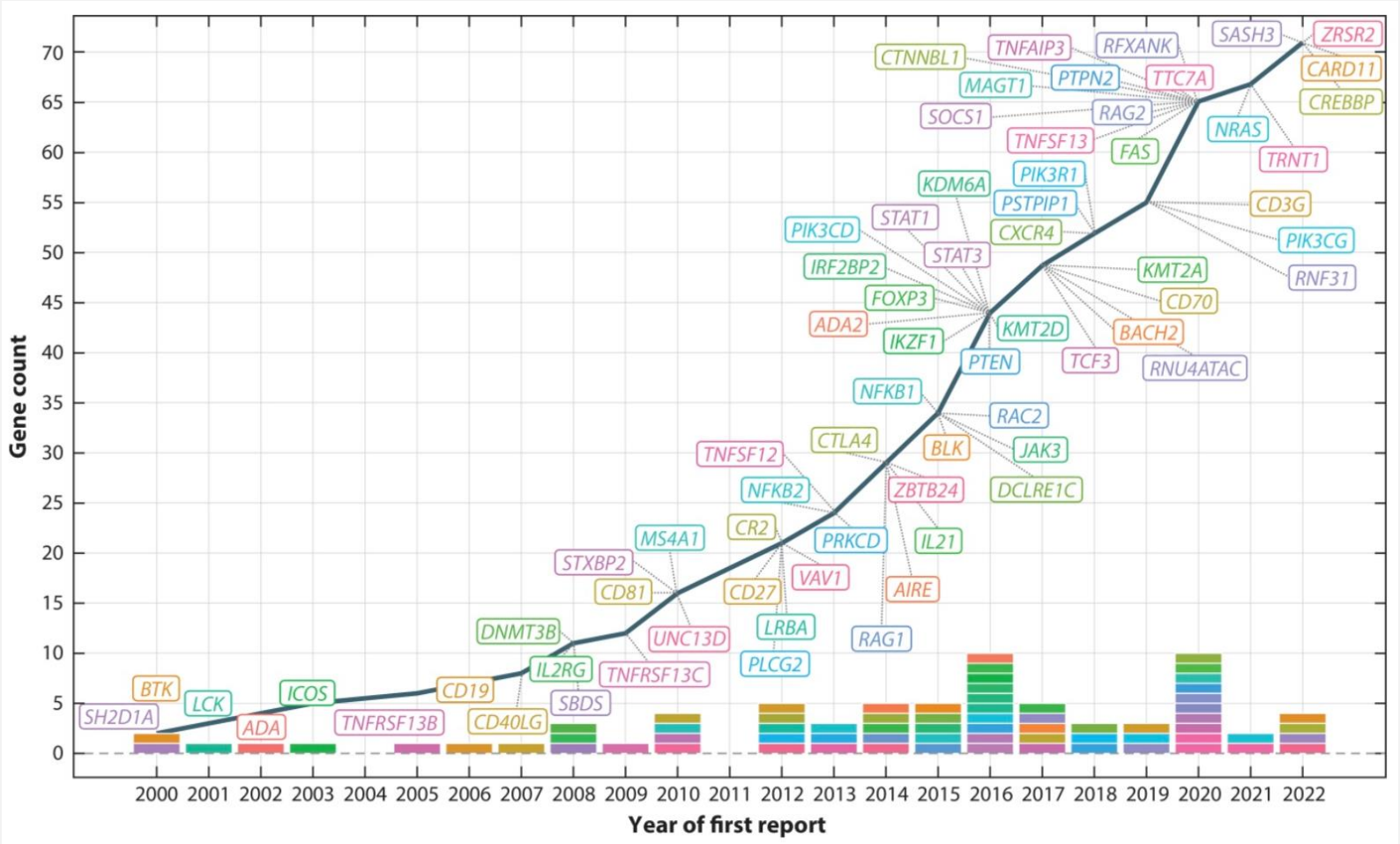
- The use of genetic testing for clinical decision-making is a recent phenomenon
- Only in the last 10-15 years have we had the ability to order a clinical test to look for changes at the DNA level to directly inform patient care

GENETIC TESTING HAS CHANGED HOW WE THINK ABOUT HUMAN DISEASE

- Expanded the clinical spectrum of known monogenic disorders
- Expanded the genetic landscape of known clinical phenotypes
- Management is informed by the combined power of genotype-phenotype information
- Study of rarer "monogenic" etiologies has informed the pathophysiology of more common and complex "polygenic" human disease

MONOGENIC ETIOLOGIES IN PATIENTS GIVEN CVID DIAGNOSES REVEAL DIVERSE PATHOLOGIES

- More than **60 monogenic CVIDs** have been identified over the last 20 years, with an additional 11 genes noted by subsequent publications to cause a CVID phenotype without explicit CVID diagnoses in the original reports



Peng et al.

DOES GENOTYPE PREDICT PHENOTYPE?

- In the US and Sweden, **those with infections only were less frequently identified (25%) to have a genetic cause** of their CVID (Abolhassani et al.)

Table 5. Genetics and clinical phenotypes

	Gene identified, n (%)	No gene identified, n (%)
United States, N = 234		
Infections only, n = 91	23 (25)	68 (75)
Complications,* n = 143	50 (35)	93 (65)
Sweden, N =113 with data		
Infections only, n = 40	11 (27.5)	29 (72.5)
Complications,* n = 73	27 (36.9)	46 (63)
Iran, N = 188 with data		
Infections only, n = 80	43 (53.7)	37 (46.2)
Complications,* n = 108	62 (57)	46 (42.5)

Abolhassani et al.

CASE

- Targeted Next Generation Sequencing Panel for Inborn Errors of Immunity identified
  - One **pathogenic variant in RAG1**, RAG1 is associated with autosomal recessive severe combined immunodeficiency

One Pathogenic variant identified in RAG1. RAG1 is associated with autosomal recessive severe combined immunodeficiency.

Additional Variant(s) of Uncertain Significance identified.

	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
RAG1	c.2689C>T (p.Arg897*)	heterozygous	PATHOGENIC
[illegible]	c.2657_2668del (p.Ala886_Pro889del)	heterozygous	Uncertain Significance
CARD11	c.3145-3C>T (Intronic)	heterozygous	Uncertain Significance
DUOX2	c.4273C>G (p.Gln1425Glu)	heterozygous	Uncertain Significance
JAK2	Gain (Exons 23-25)	copy number = 3	Uncertain Significance

Adapted from Dr. Williams, AAIFNC Annual Meeting 2025

CASE

- Additional laboratory evaluation
  - TCRvB spectratyping sent with oligoclonal T cells
  - TCRVa7.2+ T cells (0.35%) and of TCRVa7.2+CD161+ MAIT cells (0.18%) consistent with values found in RAG mutant patients
- **Hypomorphic RAG deficiency**

Adapted from Dr. Williams, AAIFNC Annual Meeting 2025

64yo male with history of Burkitt's lymphoma s/p rituximab, CVID, and benign lymphadenopathy with hypomorphic RAG1

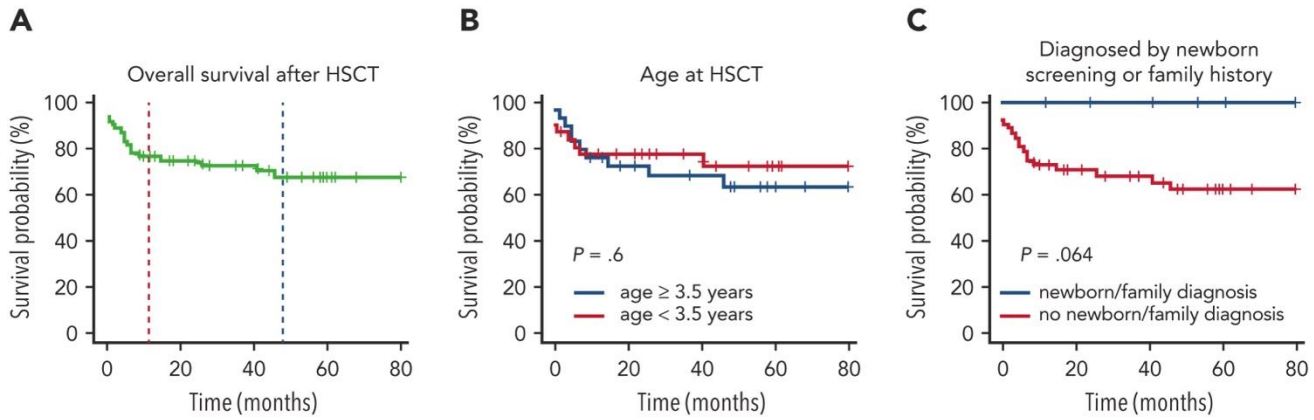
HOW DOES THIS CHANGE MANAGEMENT?

DIAGNOSIS CHANGES TREATMENT OPTIONS

- Treatment options **prior to** genetic testing
  - Immunoglobulin replacement therapy
  - Prophylactic antibiotics
- Treatment options **following** genetic testing and identification of pathogenic RAG1 variant
  - HSCT or gene therapy

Blood. 2022 Oct 27;141(7):713–724. doi: 10.1182/blood.2022017667

Hypomorphic RAG deficiency: impact of disease burden on survival and thymic recovery argues for early diagnosis and HSCT



Schuetz et al.

UTILITY OF GENETIC TESTING

- Establishing the diagnosis
- Treatment
- Prognosis
- Pre-symptomatic testing
- Screening

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- **Establishing the diagnosis**
- Treatment
- Prognosis
- Pre-symptomatic testing
- Screening

- **Establishing the diagnosis**
  - Confirming the clinical diagnosis of CVID-like disorder
  - Identifying novel presentations of other CVID-like disorders (LOCID)
  - Identifying atypical presentations of other IEIs with hypogammaglobulinemia (XLP)
  - Distinguishing genetic from acquired disorders (drug-induced hypogammaglobulinemia)

Ameratunga et. al

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- Establishing the diagnosis
- **Treatment**
- Prognosis
- Pre-symptomatic testing
- Screening

- **Treatment**
  - Offering early SCIG/IVIG treatment for individuals carrying causative mutations
  - Identifying specific treatment options
    - Abatacept for CTLA4 haploinsufficiency/LRBA deficiency
    - Leniolisib for APDS
  - Identifying patients who may benefit from HSCT or gene-based therapy
  - Can improve survival and outcomes

Ameratunga et al.

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- Establishing the diagnosis
- **Treatment**
- Prognosis
- Pre-symptomatic testing
- Screening

- **Treatment**

TABLE 3 Example of targeted therapies for patients with genetically defined primary immune regulatory disorders

Condition	Gene	Targeted therapy
IPEX	*FOXP3*	Tacrolimus Cyclosporin Sirolimus
STAT1 GOF	*STAT1*	Ruxolitinib (JAK 1/2 inhibitor) Sirolimus
STAT3 GOF	*STAT3*	Tocilizumab (IL-6 receptor blocker) Siltuximab (IL-6 blocker) Ruxolitinib (JAK 1/2 inhibitor)
LRBA deficiency	*LRBA*	Abatacept Sirolimus Hydroxychloroquine
CTLA4 haploinsufficiency	*CTLA4*	Sirolimus Abatacept
APDS	PIK3CD PIK3R1	Sirolimus Leniolisib (PI3K inhibitor)
XIAP and NLRC4	BIRC4 NLRC4	IL-18 binding protein
Primary HLH	PRF, UNC13 D STX11, STXBP2	Emapalumab (IFN-γ blocking antibody) Ruxolitinib (JAK 1/2 inhibitor)

Chandrakasan et al.

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- Establishing the diagnosis
- Treatment
- **Prognosis**
- Pre-symptomatic testing
- Screening

- **Prognosis**
  - Enables a more informed prediction of a patient's disease course
    - For those placed in an "idiopathic" group, closer and more tailored monitoring is required, in contrast to conditions where the clinical trajectory is better understood (e.g. STAT1GOF)
  - Identifies patients at higher risk for malignancy (e.g. CTLA4 haploinsufficiency) who may require closer surveillance

Ameratunga et al.

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- Establishing the diagnosis
- Treatment
- Prognosis
- **Pre-symptomatic testing**
- Screening

- **Pre-symptomatic testing**
  - Situations in which pre-symptomatic diagnosis (at any age) is not possible with protein-based tests (patients with CVID-like disorders who are asymptomatic with normal immunoglobulins)

Ameratunga et al.

UTILITY OF GENETIC TESTING IN ADULTS WITH CVID

- Establishing the diagnosis
- Treatment
- Prognosis
- Pre-symptomatic testing
- **Screening**

- **Screening**
  - Provides opportunity to screen for other at risk patients and provide family counseling

Ameratunga et al.

FINANCIAL IMPLICATIONS OF GENETIC TESTING

- One review by Elsink et al. analyzed 22 studies and found that early diagnosis of IEIs can lead to significant cost savings, ranging from **$6,500 to $108,463 per patient**, by reducing healthcare utilization and complications.
- Early identification and treatment of IEIs, result in better health outcomes, including fewer infections, hospitalizations, and emergency visits, thereby enhancing patients' quality of life.

FINANCIAL IMPLICATIONS OF GENETIC TESTING

- Another study by Sun et al. looking at cost utility of lifelong immunoglobulin replacement therapy vs. HSCT to treat agammaglobulinemia showed that **lifelong IRT costs approximately $1.51 million per patient**, significantly more than matched sibling donor (MSD) hematopoietic stem cell transplant (HSCT) at $564,000 and matched unrelated donor (MUD) HSCT at $637,000.

CONCLUSION

- **Genetic testing should be offered to all adult patients with CVID**
  - Establishes a definitive diagnosis
  - Provides a prediction of disease severity
  - Identifies patients at higher risk for malignancy who may require closer surveillance
  - Provides opportunity to screen for other at risk patients and provide family counseling
  - Increases understanding of a specific disorder and genetic mechanisms involved
  - Reduces healthcare utilization and complications
  - **Can identify new potential therapeutic targets**
  - **Can improve survival and outcomes**

THANK YOU

REBUTTAL

COST CONCERNS

- Genetic testing can be expensive, especially for those without insurance coverage
- The cost of testing may be prohibitive for some individuals
  - **While cost has historically been a barrier, the price of genetic testing has decreased significantly over the past decade due to advances in technology and increased demand.**
    - Many tests now cost only a few hundred dollars, and some are even available at low or no cost through research programs or nonprofit initiatives.
  - **Additionally, early detection through genetic testing can prevent more costly medical interventions later by enabling proactive care, ultimately reducing overall healthcare spending.**

WHEN COMPARED TO THE COST OF AN EPIPEN…

- 🧬 **Genetic Testing (One-Time Cost)**
  - Basic panel (PID-specific): $100–$1,000
  - Comprehensive panel (hundreds of genes): $1,500–$2,000
  - Whole Exome Sequencing (WES): $2,000–$5,000
  - 👉 **Average cost range for relevant testing**: **$1,000–$2,000** one-time
- 💉 **EpiPen (Ongoing Annual Cost)**
  - Typical prescription: 2 pens per pack
  - Cost (without insurance): $300–$700 per 2-pack (brand-name EpiPen)
  - Generic alternatives: ~$150–$300 per 2-pack

WHEN COMPARED TO THE COST OF AN EPIPEN…

- Assuming:
  - **1 two-pack per year** (conservative use)
  - **Life expectancy**: ~80 years
  - **Starting age**: ~10 years old
  - 👉 **70 years of use × $150–$700 per year** = **$10,500 – $49,000** over a lifetime

Category	Cost Estimate
Genetic Testing (one-time)	**$1,000 – $2,000**
EpiPen (lifetime, 1 pack/year)	**$10,500 – $49,000**

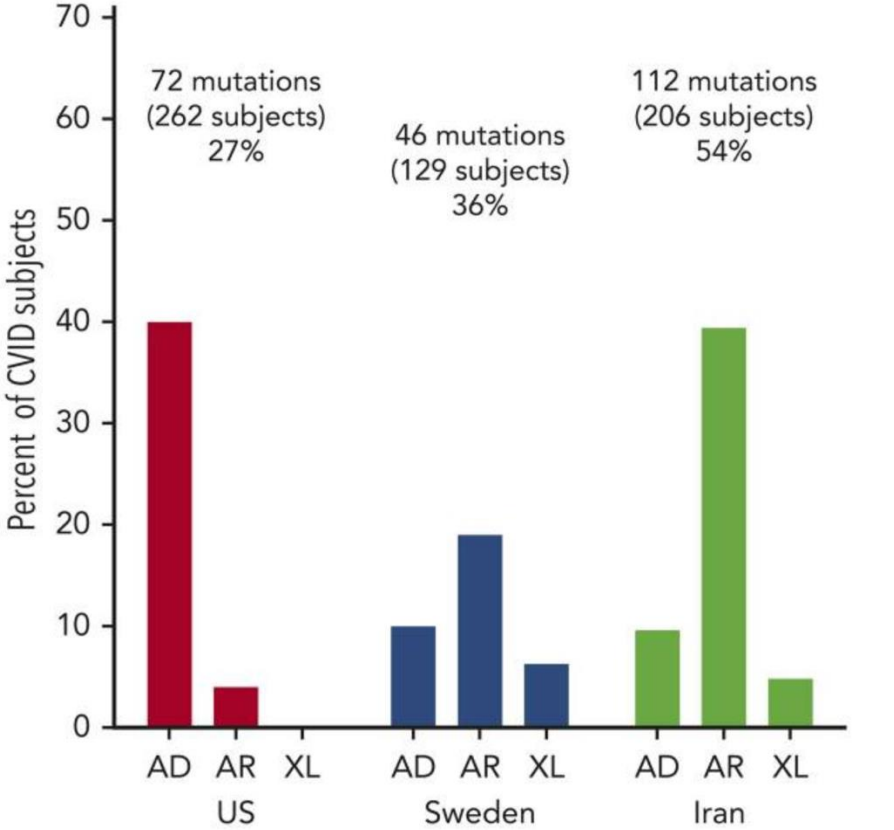
INTERPRETING UNCERTAIN RESULTS

- Genetic testing may uncover VUSs, genetic variants with no established clinical significance for the disease
- These VUSs can leave clinicians and individuals uncertain about the implications of genetic findings

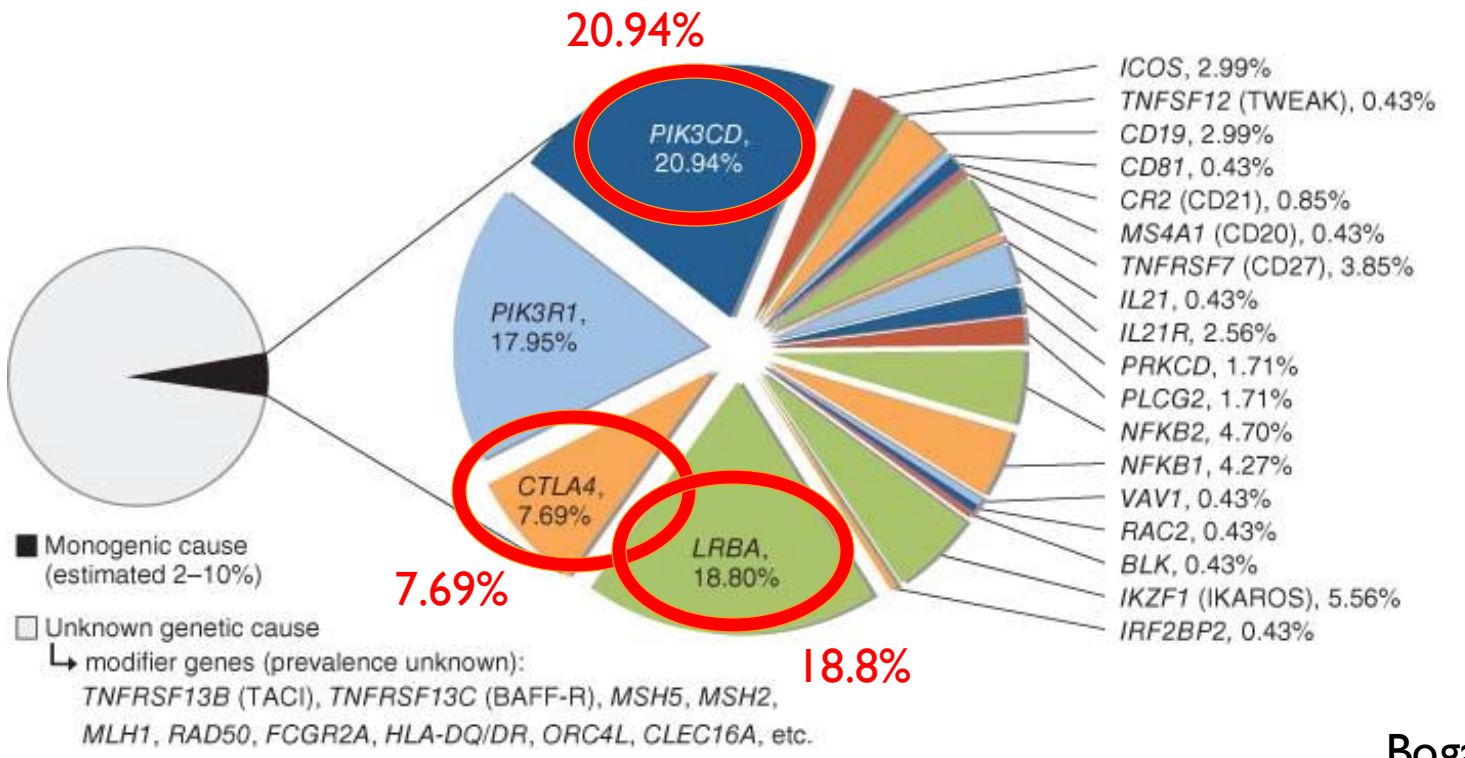
DISEASE-CAUSING GENES UNDERLYING AN IMMUNE DEFECT PRESENTING AS CVID

Whole-exome analyses in 3 different CVID patient groups from 3 different continents revealed **68 known disease-causing genes** underlying an immune defect presenting as a CVID syndrome (Abolhassani et. al).

27% of individuals in the US with a CVID diagnosis were found to have disease-causing genes, even higher percentages in Sweden and Iran



Abolhassani et al.



>47% of the monogenic causes have targeted therapy available

Bogaert et. al

MOLECULAR GENETICS OF CVID

INTERPRETING UNCERTAIN RESULTS

- **It's true that genetic tests can reveal uncertain findings, but they don't necessarily complicate care.**
  - As medical professionals, we are trained to interpret these results carefully and typically do not base major decisions on VUSs. Instead, these are the patients we know to follow more closely.
- **As our understanding of genetics grows, many VUSs are later reclassified, meaning the value of your genetic information can increase over time.**

EMOTIONAL AND PSYCHOLOGICAL IMPACT

- Inconclusive results or even a positive result can increase stress and anxiety for individuals and their families.
- Negative results may not rule out all possibilities and could lead to further investigations, adding to the stress.
- **Genetics testing also provides clarity, control, and the opportunity for informed decision-making.**
  - For many individuals, simply having more information (positive, negative, or inconclusive) can reduce uncertainty and provide a clearer path forward. Access to genetic counseling is also a key part of the process, offering support to help individuals and families understand and cope with their results.
- **Ultimately, the insight gained empowers people to make proactive health choices and better prepare for the future, which can reduce long-term anxiety.**

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