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Genetic Testing is NOT indicated in the routine evaluation of CVID in adult patients

Chang Su, PGY4

UCSF

Case

- 80-year-old man, hx of CLL (in remission >40 years) and otherwise healthy, had a CXR-confirmed bacterial pneumonia for the first time that he can remember. He was hospitalized x3 weeks.
- Incidentally found to have IgG 388 and was referred to immunology for further evaluation.
- We found that his IgG remains in the 300-400 range, IgA was low but not undetectable, IgM & IgE were normal, and pneumococcal titers 0/23+ -> 0/23+ post PPSV23 & PCV21.
- He was diagnosed with CVID.
- No other infections, no autoimmunity, no malignancy > 40 years

Is this a patient you would offer genetic testing?

Outline

Routine genetic testing is not recommended by guidelines

Limited utility in guiding management

High stress & cost on healthcare system

Negative psychological impact and social implications for patients

Outline

Routine genetic testing is not recommended by guidelines

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Routine genetic testing is not recommended by International Consensus Document (ICON) on CVID

Summary:

"Despite the fact that several monogenic defects underlying apparent CVID have been defined, because of the rarity of each defect and the lack in most cases of significant impact on management, as well as the cost of testing, **genetic studies are not considered appropriate for routine use in patients with CVID at this time**"

Diagnostic criteria:

"**Genetic studies** to investigate monogenic forms of CVID or for disease-modifying polymorphisms **are not generally required for diagnosis and management in most of the patients**, especially those who present with infections only without immune dysregulation, autoimmunity, malignancy, or other complications."

Bonilla et al. 2015

Routine genetic testing is not recommended by Practice Parameter for the diagnosis and management of primary immunodeficiency

Summary statement 85. The diagnosis of CVID should be considered in male or female subjects older than 4 years who have low IgG and IgA levels and impaired antibody response but **do not have genetic lesions** or other causes of primary or secondary antibody deficiency. (C)

Bonilla, et al. 2015

Italian Primary Immunodeficiency Network Consensus does not support population-based genetic testing

Statements	Level of agreement (%)	Level of disagreement (%)	Neutral	Score (Mean ± SD)
Genetic testing should be used for large-scale, population-based screening.	11	78	11	-0.47 ± 0.45
Diagnosis is suggested by positive functional test result	89	0	11	0.76 ± 0.35

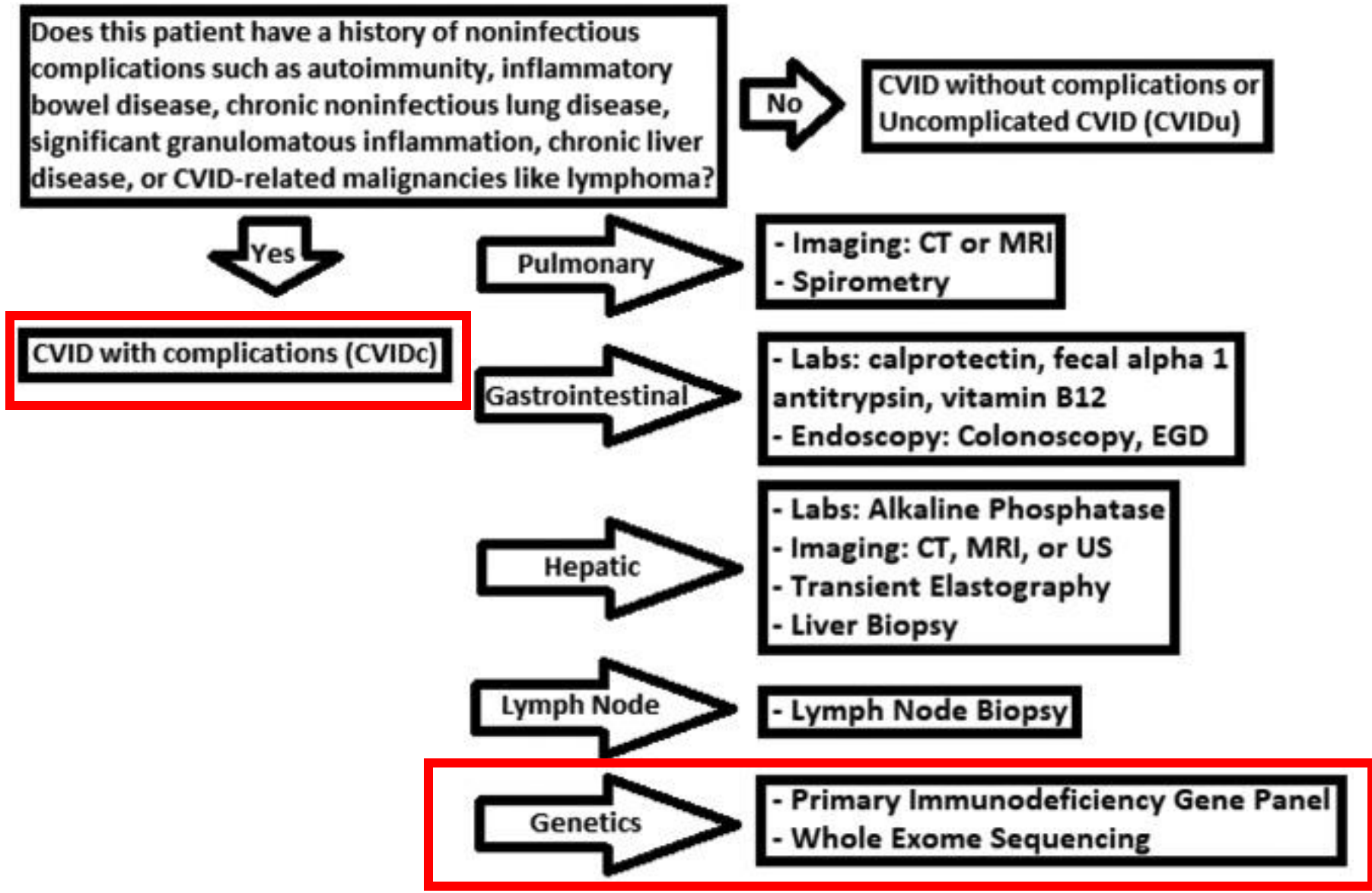
Giardino et al. 2024

CVID is a clinical diagnosis & heterogenous
No pathogenic variants are identified in most cases

- Clinical diagnosis as previously reviewed
- Heterogenous nature
  - Clinical heterogeneity: asymptomatic to significant complications (autoimmunity, malignancy)
  - Genomewide association study of 360 patients with CVID identified multiple potential susceptibility loci for CVID
- Pathogenic variants are NOT identified in ~70%-80% of patients, likely higher percentage in adults without complications

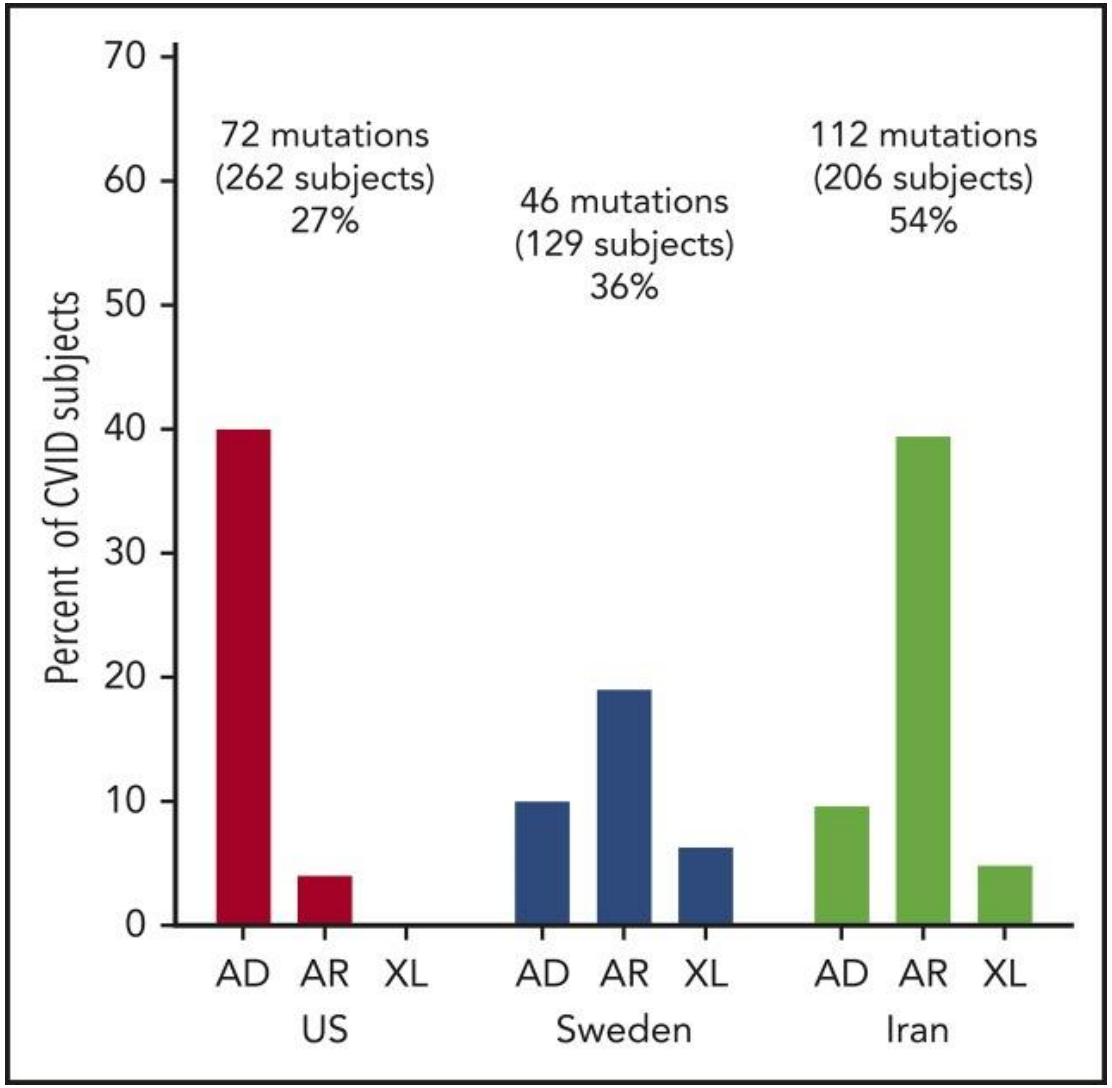
Bonilla et al. 2015, Ameratunga et al. 2023

Genetic testing is only indicated in CVID with complications



Lee et al. 2021

Clinical patterns did not correlate with specific gene defects



Abolhassani et al. 2020

No pathogenic variants are identified in most cases with complications

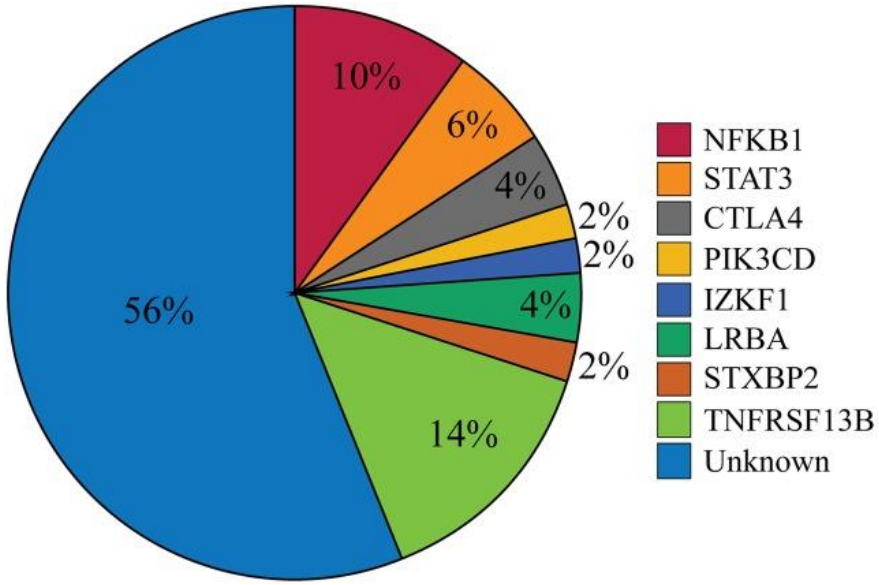
	Gene identified, n (%)	No gene identified, n (%)
United States, N = 234		
Infections only, n = 91	23 (25)	68 (75)
Complications,* n = 143	50 (35)	93 (65)
Sweden, N =113 with data		
Infections only, n = 40	11 (27.5)	29 (72.5)
Complications,* n = 73	27 (36.9)	46 (63)
Iran, N = 188 with data		
Infections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

64% Consanguinity

Abolhassani et al. 2020

No pathogenic variants are identified in most cases with complications

- 50 patients with CVID with early-onset, inflammatory, or autoimmune complications
- WES identified 17 probably disease-causing mutations in 15 patients (30%)



Maffucci et al. 2015

Summary:

Routine genetic testing is not recommended by guidelines

- Routine genetic testing for CVID is not recommended by ICON on CVID or the practice parameter for PID
- Italian PID network consensus does not support large-scale, population-based genetic testing
- CVID is a clinical diagnosis that does not require genetic testing
- No pathogenic variants are identified in most cases (70-80%)
- Genetic testing is recommended in cases with complications but even in cases with complications, no pathogenic variants are identified in most cases (~60-70%)

Outline

Routine genetic testing is not recommended by guidelines

Limited utility in guiding management

High stress & cost on healthcare system

Negative psychological impact and social implications for patients

Management might not change based on genetic lesions identification according to Practice Parameter for PID

Summary statement 87.

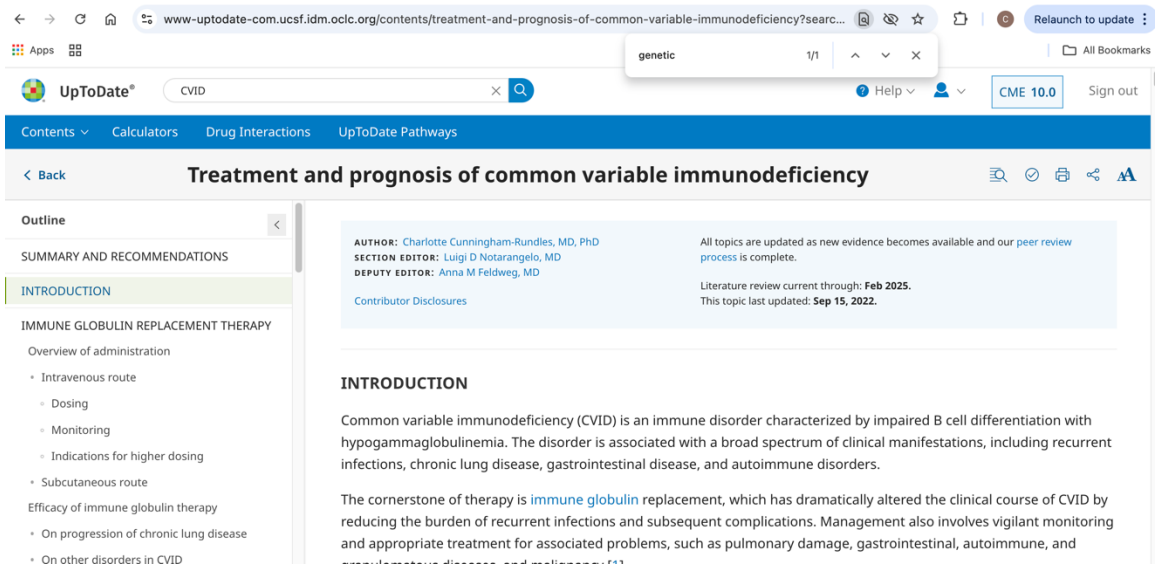
The clinical utility of identifying these (genetic/molecular) mutations in patients given a diagnosis of CVID is not entirely clear

Management might not change as a result of the identification of one of these specific genetic lesions.

Bonilla, et al., 2015

UpToDate article on management of CVID does not hinge on genetic testing

- UpToDate article on the management/prognosis of CVID:
  - Immune globulin therapy/IgG replacement
  - Antibiotics use – prophylactic & treatments
  - Vaccination
  - Autoimmune & inflammatory disorders
  - Monitor for malignancy



Cunningham-Rundles, 2025

Management of CVID focuses on complications rather than genetic mutations

Other than IgG-RT:

- Autoimmune cytopenia: Rituximab
- IBD: low-dose steroids, azathioprine, 6-mercaptopurine, infliximab (anti-IL 12), ustekinumab (IL-23), vedolizumab
- Granulomatous disease: TNF-a inhibitors, rituximab +/- azathioprine, 6MP or mycophenolate mofetil

INVITED REVIEW | Full Access

Common variable immune deficiency: Dissection of the variable

Charlotte Cunningham-Rundles

Cunningham-Rundles, 2019

Summary

Limited utility in guiding management

- According to the 2015 PID practice parameters, identification of genetic lesions may not change management
- Management of CVID does not hinge on genetic testing, and focuses on IgG-RT and therapies targeting complications

Outline

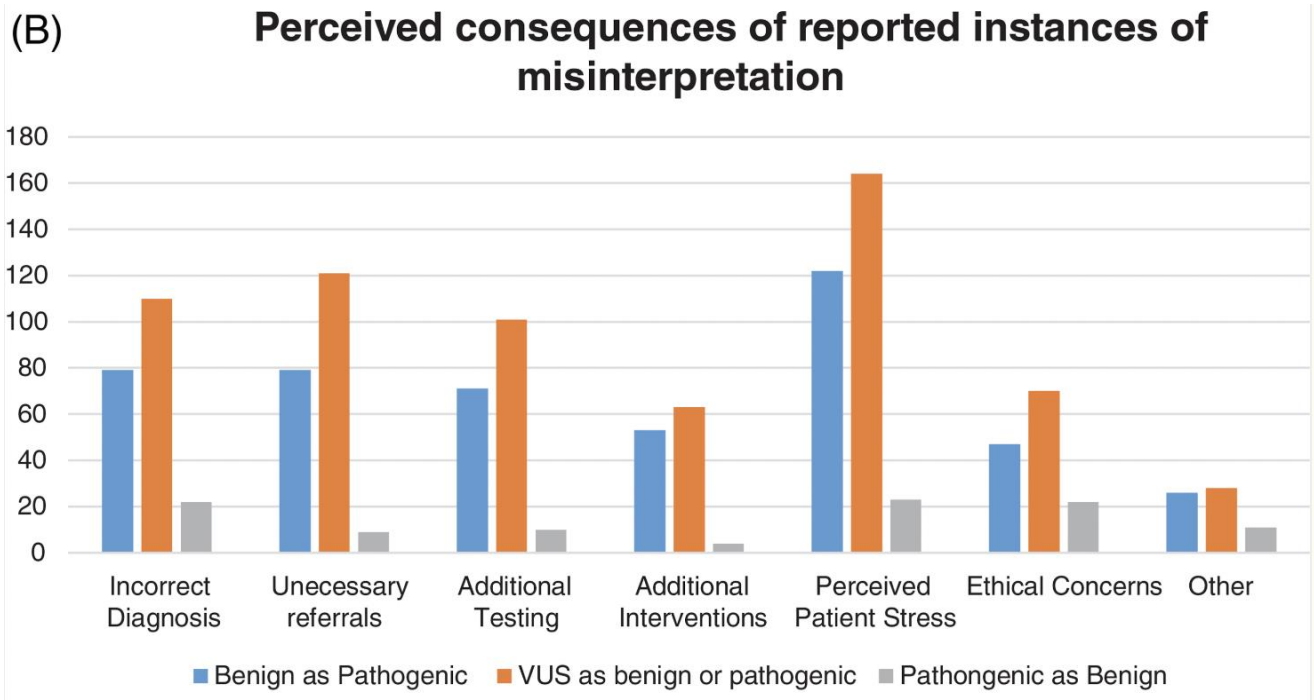
Routine genetic testing is not recommended by guidelines

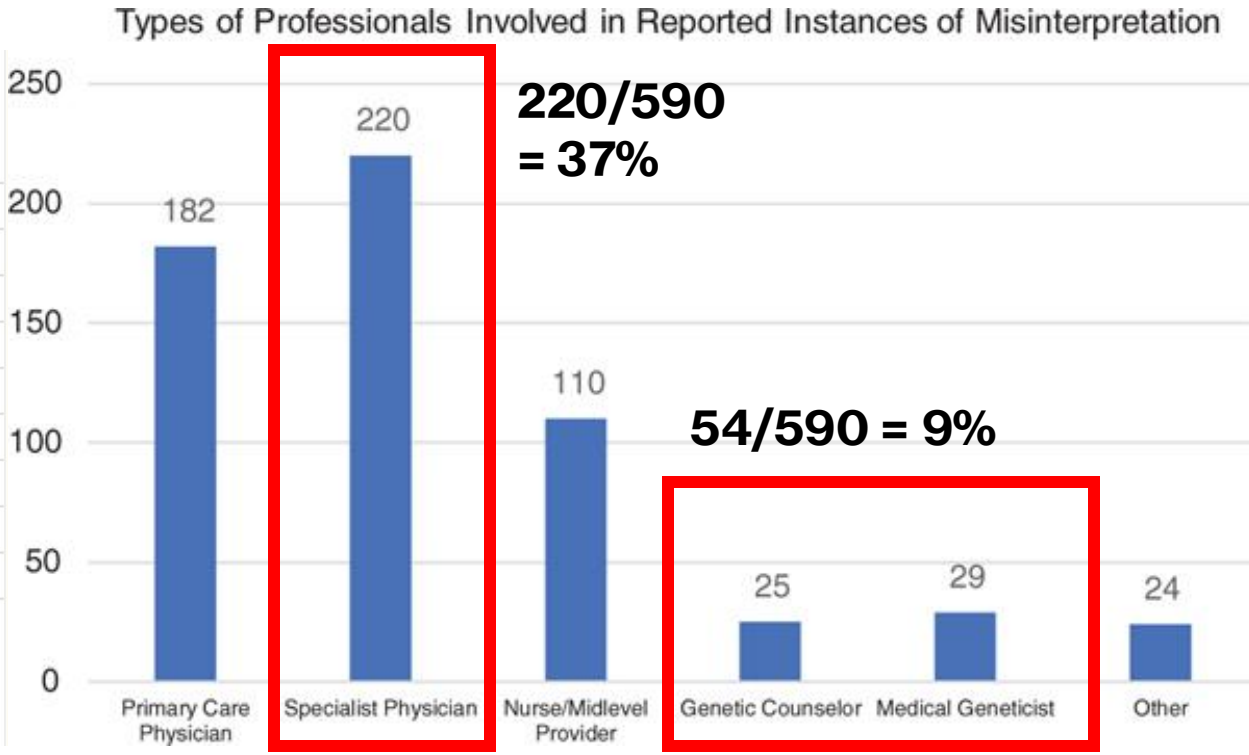
Limited utility in guiding management

High stress & cost on healthcare system

Negative psychological impact and social implications for patients

Most (83%, 299/360) genetic professionals reported they were aware of ≥1 example of misinterpretation of a genetic testing result





AI

Genetic counselors/ Geneticist

Donohue et al. 2021

Show of hands –

Do you have formal training in genetics/counseling?

Are you confident in providing comprehensive & accurate genetic counseling?

Do you have access to a genetic counselor?

Trigger warning – discussing genetic testing results can be challenging, esp. VUS

- American College of Medical Genetics and Genomics guidelines: 'A VUS should not be used in clinical decision making.'
- Are you ready to discuss a **28-page** Invitae report including **22 variants (16 VUS)** with the patient routinely?
- Recontact obligation when VUS are reclassified

Hoffman-Andrews et al, 2017; Scribd 2021

RESULT: CARRIER

One Pathogenic variant identified in BTD. BTD is associated with autosomal recessive biotinidase deficiency.

One Pathogenic variant identified in MECR. MECR is associated with autosomal recessive childhood-onset dystonia with optic atrophy and basal ganglia abnormalities.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BTD	c.1330G>C (p.Asp444His)	heterozygous	PATHOGENIC
MECR	c.772C>T (p.Arg258Trp)	heterozygous	PATHOGENIC
AHI1	c.2962-3T>C (Intronic)	heterozygous	Uncertain Significance
ARFGEF2	c.1190+6C>T (Intronic)	heterozygous	Uncertain Significance
ATP1A2	c.311T>C (p.Ile104Thr)	heterozygous	Uncertain Significance
B4GALT7	c.185G>A (p.Arg62Lys)	heterozygous	Uncertain Significance
CC2D2A	c.566A>G (p.Glu189Gly)	heterozygous	Uncertain Significance
CCER2	c.757_759del (p.Lys253del)	heterozygous	Uncertain Significance
CYP7B1	c.850+5G>C (Intronic)	heterozygous	Uncertain Significance
DYNC2H1	c.10669T>C (p.Ser3557Pro)	heterozygous	Uncertain Significance
FAM126A	c.1504A>G (p.Met502Val)	heterozygous	Uncertain Significance
IDH3A	c.742G>A (p.Val248Ile)	heterozygous	Uncertain Significance

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
LAMA2	c.922G>A (p.Glu308Lys)	heterozygous	Uncertain Significance
MCCC2	c.1657A>G (p.Ile553Val)	heterozygous	Uncertain Significance
MFSD8	c.1136T>C (p.Phe379Ser)	heterozygous	Uncertain Significance
PC	c.1151C>T (p.Ala384Val)	heterozygous	Uncertain Significance
PIGN	c.1004C>T (p.Pro335Leu)	heterozygous	Uncertain Significance
UPB1	c.143C>G (p.Ser48Cys)	heterozygous	Uncertain Significance
ACADS	c.625G>A (p.Gly209Ser)	heterozygous	Benign (reportable variant)
CHIT1	c.304G>A (p.Gly102Ser)	heterozygous	Benign (reportable variant)
FAH	c.1021C>T (p.Arg341Trp)	heterozygous	Benign (Pseudodeficiency allele)
GALC	c.1685T>C (p.Ile562Thr)	heterozygous	Benign (Pseudodeficiency allele)

About this test

This diagnostic test evaluates 1577 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

High stress on physicians

- Lack of formal training in genetics
- Coordination and cooperation between specialists and organization of care as a team
- Discovering hereditary pattern incidentally
- The enigmas posed by the diverse effects of genetic research (VUS) that raise uncertainties

Pasquier et al. 2022

Cost is very high

- Cost: ~$100 (with insurance) - $4000 (out-of-pocket for whole exome trio)
  - Invitae PID panel increased the lowest tier out-of-pocket cost to $299 (from $250 in 2024)
- Frequency of CVID in the US: 1:25,000 to 1:50,000
- US population ~340 million

340 Million X 1:25,00-1:50,000 X $299 = **$ 2-4 Million**

X $4000 = **$ 27.2-54.4 Millions**

Ameratunga et al. 2023

Summary

High stress & cost on healthcare system

- Most genetic professionals reported they were aware of ≥1 example of misinterpretation of a genetic testing result, mostly from specialty physicians and include from medical geneticists/genetic counselors
- High stress on physicians physically, mentally and emotionally
- VUS can be particularly challenging
- Cost is very high ($54 millions a year)

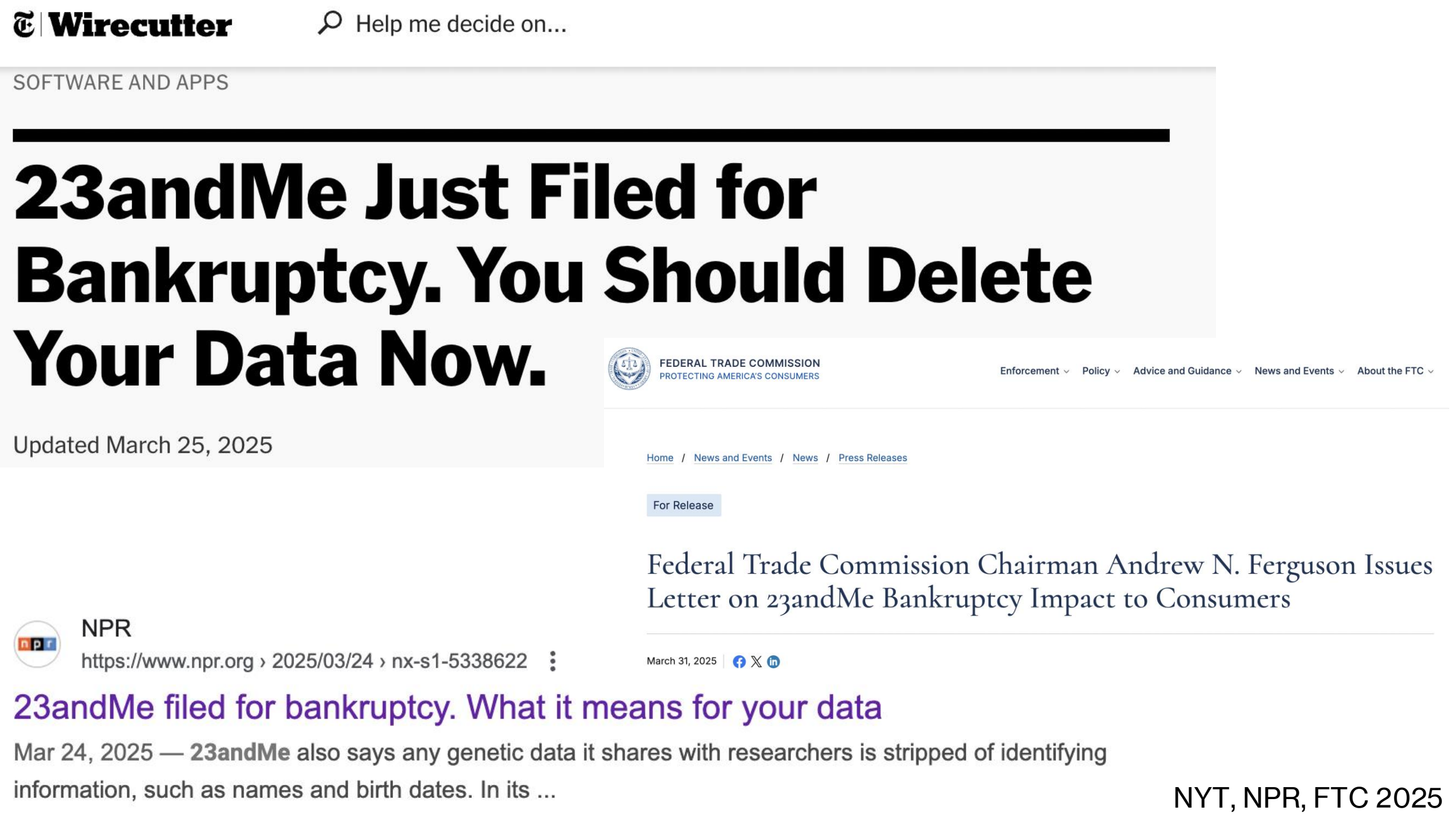
Outline

Routine genetic testing is not recommended by guidelines

Limited utility in guiding management

High stress & cost on healthcare system

Negative psychological impact and social implications for patients



NYT, NPR, FTC 2025

Concerns re: privacy breach & genetic discrimination remains high

Limited coverage of Genetic Information Nondiscrimination Act (GINA) 2008:

- **NO** coverage of life insurance, disability insurance, long-term care insurance or other forms of protection commonly desired by individuals at risk for a genetic disorder.
- Does **NOT** apply to people getting insurance through the federal government or the military

Genetic discrimination are present

- Meta-analysis of 42 studies from 1996-2014: All studies showed concerns about genetic discrimination are present in the studied population

Wauters et al 2016, Hoffman-Andrews el al, 2017

VUS takes a toll on patients

- Interview of 11 patients: primary concern with VUS uncertainty involves personal and practical issues as they directly inform health-care decisions
- Giving a VUS result has been described as putting patients in **'genetic purgatory'**
- VUS in has been called **'toxic knowledge'** for the high emotional burden of uncertainty
- Participant 9: "I thought that was the point of doing this was...that they knew what it was. It was a little frustrating to have them say that we don't know what it is..."

Hoffman-Andrews el al, 2017; Parens & Appelbaum 2019

Summary

Negative psychological impact and social implications for patients

- Concerns for privacy breach and genetic discrimination remains high
- GINA 2008 only provides limited coverage
  - **No** coverage on life insurance, disability insurance or long-term care insurance
  - **No** coverage for military/veteran/anyone receiving government insurance
- VUS is challenging for patients, personally & practically

Case continued

- 80-year-old man, hx of CLL (well controlled >40 years) and otherwise healthy, had a CXR-confirmed bacterial pneumonia for the first time that he can remember. He was hospitalized x3 weeks. Pneumonia was thought most likely due to aspiration. He has been working with SLP to gradually advance his diet.
- IgG remains in the 300-400 range, IgA was low but not undetectable, IgM & IgE were normal, and pneumococcal titers 0/23+ -> 0/23+ post PPSV23 & PCV21.
- Shared decision making was to not start IgG-RT
- No infection, autoimmunity or new malignancies 1 year since diagnosis

Is this a patient you would offer genetic testing?

Genetic Testing is NOT indicated in the routine evaluation of CVID in adult patients

Routine genetic testing is not recommended by guidelines

Limited utility in guiding management

High stress & cost on healthcare system

Negative psychological impact and social implications for patients

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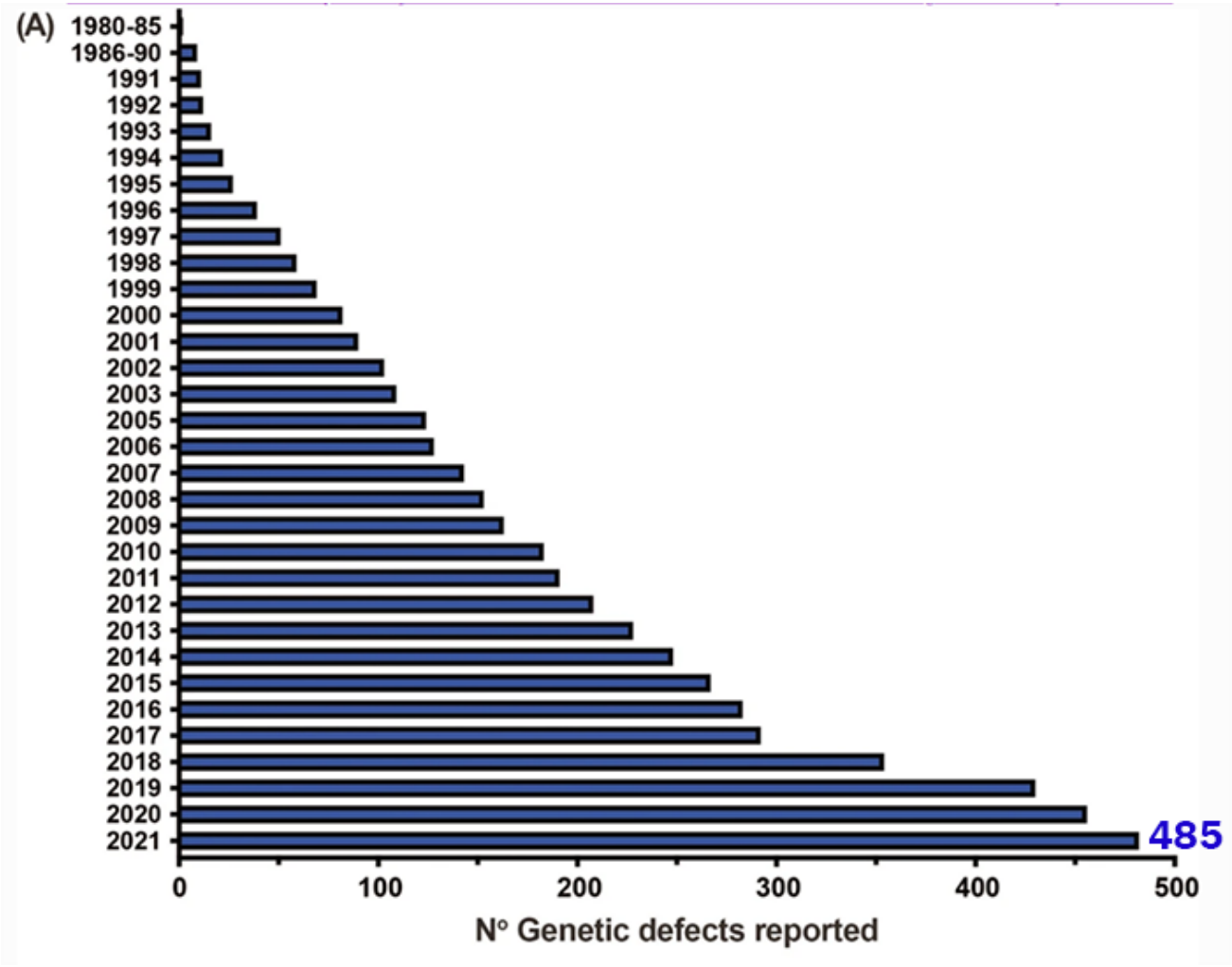
Genetic Testing is NOT indicated in the routine evaluation of CVID in adult patients
Rebuttal

Chang Su, PGY4

UCSF

List of genetic variants that cause primary immunodeficiency expands



The number of genetic variants known to cause IEI/PI by year.

Tangye, et al.

How often are we going to re-test if the genetic testing does not change management now?

TABLE I. Mutations of genes predisposing to or modifying disease severity of CVID*

Gene symbol	Synonym	OMIM gene	OMIM phenotype	Inheritance	HGNC ID	Gene name (HGNC)	MANE select RefSeq transcript	MANE select RefSeq protein
MSH5		603382	137100	AD, AR	7328	mutS homolog 5	NM_172166.4	NP_751898.1
MSH6		600678	NA	AR	7329	mutS homolog 6	NM_000179.3	NP_000170.1
NOD2	CARD15	605956	NA		5331	Nucleotide-binding oligomerization domain–containing 2	NM_001370466.1	NP_001357395.1
TNFRSF13C	BAFFR	606269	613494	AR	17755	TNF receptor superfamily member 13C	NM_052945.4	NP_443177.1
TNFSF10	TRAIL	603598	NA		11925	TNF superfamily member 10	NM_003810.4	NP_003801.1
TNFSF12	TWEAK	602695	NA	AR	11927	TNF superfamily member 12	NM_003809.3	NP_003800.1
TNFSF13	APRIL	604472	NA	AR	11928	TNF superfamily member 13	NM_003808.4	NP_003799.1
TNFRSF13B	TACI	604907	240500	AD, AR	18153	TNF receptor superfamily member 13B	NM_012452.3	NP_036584.1

AD, Autosomal dominant; *AR*, autosomal recessive; *CVID*, common variable immunodeficiency disorders; HGNC, HUGO Gene Nomenclature Committee; *MANE*, Matched Annotation from NCBI and EMBL-EBI identifiers for transcript and protein; *NA*, not available; OMIM, Online Mendelian Inheritance in Man.

*It is possible with further information that some of these mutations may be considered causative in the future.

"*It is possible with further information that some of these mutations may be considered causative in the future"

Ameratunga et al. 2023

Management rarely change based on genetics . Targeted therapy is extremely expensive.

8 billion (population) X 1:25k-1:50k (CVID frequency) = 160-320k people w/ CVID

Gene defect	Clinical manifestation	Treatment	Cost/ year	# Cases reported to date
LRBA LoF	Hepatosplenomegaly, immune-mediated cytopenia, organ-specific autoimmunity, chronic diarrhea	Abatacept	19-46k	212 by 2021
CTLA4 LoF	Hypogam, diarrhea, enteropathy, ILD, lymphocytic organ infiltration, splenomegaly	Abatacept	19-46k	222 by 2021
STAT3 GoF	Autoimmune hemolytic anemia/thrombocytopenia, enteropathy, DM-1, lymphadenopathy, hepatosplenomegaly	Jakinibs; Tocilizumab	50-70k; 26-72k	~70 by 2024
PIK3CD GoF	Benign lymphoproliferation, GI disease, bronchiectasis, autoimmune cytopenia, glomerulonephritis, arthritis, colitis	Sirolimus; Idelalisib	1-10k; 150-180k	<100 by 2018

Ameratunga et al. 2023, Lee et al. 2021, Jamee et al. 2021, Zhou et al. 2024, Zhang et al. 2019

n=235, US cohort

Genetic mutation identified in ~1/3 on WES.

Targeted therapy in ~1/20.
CTLA4 - 4, STAT3 - 3, LRBA – 2, PIK3CD - 2

Genes found	Gene name	Inheritance	No.
TACI/TNFRSF13B	Transmembrane activator and CAML interactor	AD	27
NFKB1	Nuclear factor κ B subunit 1	AD	13
CTLA4	Cytotoxic T-lymphocyte associated protein 4	AD	4
KMT2D	Lysine methyltransferase 2	AD	4
IKZF1	IKAROS family zinc finger 1	AD	3
PIK3CD	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit Δ	AD	3
STAT3	Signal transducer and activator of transcription 3	AD-GOF	3
LRBA	Lipopolysaccharide-responsive beige-like anchor protein	AR–Comp Het	2
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	AR–Comp Het or AD	2
TCF3	Transcription factor 3	AD	2
CXCR4	C-X-C motif chemokine receptor 4	AD	2
NFKB2	Nuclear factor κ B subunit 2	AD	1
CARD11	Caspase recruitment domain family member	AD	1
RAG1/RAG2	Recombination activating ½	AR–Comp Het	1
BACH2	BTB domain and CNC homolog 2	AD	1
LIG4	DNA ligase 4	AR-Hom	1
STXBP2	Syntaxin-binding protein 2	AR-Comp Het	1
CD40L	CD40 ligand	XL	1
LIG1	DNA ligase 1	AR–Comp Het	1
RTEL1	Regulator of telomere elongation helicase 1	AR–Comp Het	1

Abolhassani et al. 2020

Before you say that genetic testing is indicated in the routine evaluation of CVID in adult patients, what do you mean by routine genetic testing?

- What kind of testing? Single gene, 23&me, PID panel, whole exome/genome?
- When do you test? At diagnosis, 5 or 50 years into diagnosis? What about all the people who did not get testing at diagnosis? Do we test them all now?
- How often do you test? One test one time, yearly, every time a new gene gets discovered?

When a reclassifications inevitably happen, who is responsible for the clinical consequences?

:er, and her daughters Tricia Leigh, right, and Katy Mathes. ALYSSA SCHUKAR FOR THE WALL STREET JOURNAL

By Amy Dockser Marcus Follow
Dec. 20, 2019 11:43 am ET

Rashkin, et al. 2023

Genetic testing has implications for decades. False negative can be worse than no testing at all.

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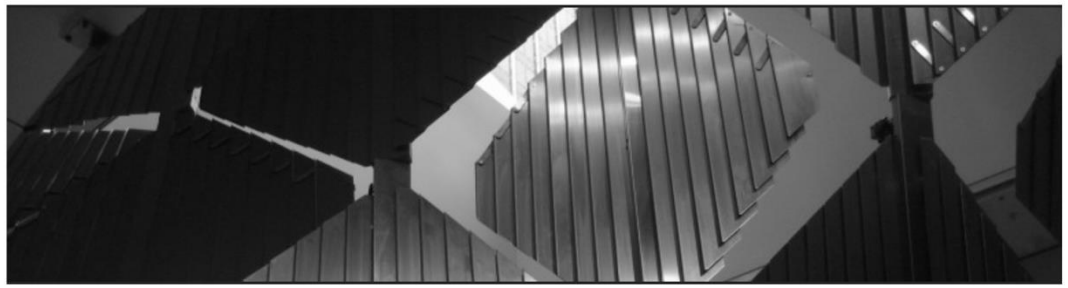

← When Good Genetic Counselors Are Bad Role Models

Bias In The Genetic Counseling Profession: Reimagining The Certification Exam →

BY ROBERT RESTA | NOVEMBER 18, 2020 · 10:27 PM

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What A Mess

The single biggest problem in communication is the illusion that it has taken place. – Apocryphal quote, likely incorrectly attributed to George Bernard Shaw

A South Carolina court recently granted a summary judgment in favor of the defendant in the case of *Williams v. Quest Diagnostics, Inc., Athena*

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Lawyers: what you can be sued for when genetic info is integrated into clinical care:

- Over testing and incomplete information
- Choice of specific panels or tests
- Inappropriate use of or reliance on a test
- Incorrect variant calls
- Faliure to communicate results to patients accurately
- Failure to communicate results & share data with clinicians within a health care system
- Failure to analyze and offer incidental findings or secondary results
- Failure to update and recontact
- Failure to warn family members
- Error and failures in direct-to-consumer testing

Marchant, et al. 2020, AMA 2023

GINA (2008) is limited, and legislation does not ease concerns about genetic discrimination

- Genetic Information Nondiscrimination Act (GINA) of 2008 limitations:
  - Limited monetary sanctions: maximum of $500,000 per violation
  - Legal ways for employers to access health information: e.g. Wellness program, preemployment consent for a release of all medical records
  - Any policy can change at any point
- Exclusive protection for genetic information in legislation does not appear to be an appropriate answer to concerns about genetic discrimination

Erwin et al. 2008, Wauters et al. 2016

Summary

- In the US, genetic mutation is identified in 30% of CVID cases, but targeted therapy is available for only ~5%. Overall, management rarely change based on genetic testing.
- Targeted therapy can be cost-prohibitive.
- A negative testing can have worse clinical consequences than no testing at all.
- For everyone who had negative testing, are you going to re-test? How often?
- Who is responsible for the clinical consequences due to reclassification?
- Genetic testing can have clinical & legal implications for decades.
- GINA is limited and can change any time. Legislation does not ease concerns about genetic discrimination.

Genetic Testing is NOT indicated in the routine evaluation of CVID in adult patients

Routine genetic testing is not recommended by guidelines

Limited utility in guiding management

High stress & cost on healthcare system including legal implications.

Negative psychological impact and social implications for patients

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