PACIFIC COAST REPRODUCTIVE SOCIETY

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INNOVATION AND INTEGRATION

THE FUTURE OF REPRODUCTIVE MEDICINE

Weathering Turbulence in the Genetics Industry: Management of Expanded Carrier Screening Panels

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Disclosure Slide

- I am a full-time employee/stockholder at CooperSurgical, Inc.

Expected Learning Outcomes

- Review current professional society guidelines and industry practices as they relate to carrier screening.
- Discuss the current commercial landscape of expanded carrier screening offerings and how recent events have shifted clinical practices and operations.
- Examine considerations and potential best practices around expanded carrier screening including how/if these practices may translate to third-party reproduction.

Today, I'd like to address:

Why has carrier screening gotten increasingly more complex, and how can we try and weather the storm?

How do we try and evaluate the clinical utility of carrier screening?

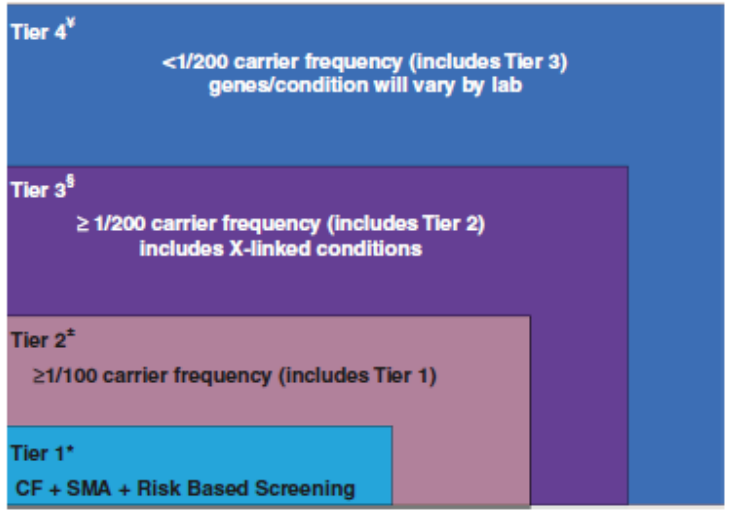
What does the future of carrier screening look like?

#1: Conflicting professional guidelines

- Goal: To identify individuals or couples that are at-risk to have a child with an autosomal recessive (AR) or X-linked (XL) disorder
- ACOG vs. ACMG recommendations
  - ACOG: Cystic fibrosis, spinal muscular atrophy, hemoglobin disorders, fragile X (select indications), Ashkenazi Jewish disorders (ethnicity-specific)
  - ACMG: “Tier 3” panel (113 AR and XL disorders), “Tier 4” panel for select indications
- ASRM donor recommendations: CF, SMA, hemoglobinopathies, fragile X (oocyte), expanded carrier screening “may also be appropriate”

ACMG recommends:

- The phrase “expanded carrier screening” be replaced by “carrier screening”.
- Adopting a more precise tiered system based on carrier frequency (Fig. 1).



#2: Instability in the genetic testing industry

BY KATIE STOLL | SEPTEMBER 26, 2022 - 5:02 PM

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Unprofitable Genetic Testing Labs – The Size of the Loss, The Reasons for the Loss, and What It Means for Genetic Counseling and Genetic Counselors

By Katie Stoll, MS, Jessie Conta, MS, and Michael Astion, MD, PHD

Genetic counseling is a critical part of the genetic services process, beyond just coordination and ordering of a genetic test. However, as the genetic counseling profession has grown alongside the expansion of genetic testing, it has become increasingly intertwined with and dependent upon the financial success of commercial genetic testing laboratories. The relationship risks undervaluing genetic counseling and the breadth of the services genetic counselors provide.

The genetic testing industry has seen rapid growth over the past two decades, with many new companies and billions of dollars invested into start-up genetic testing labs. Despite the enthusiasm of venture capitalists and other investors, commercial genetic testing labs are largely unprofitable, and the losses are significant and sustained. This is shown in Tables 1 and 2 below which are derived from analyzing publicly available, quarterly and annual financial reports (10-Q and10-K Filings) of publicly traded companies whose primary business is clinical genetic/genomic testing.

Table 2

Net profit (loss) for seven publicly traded genetic testing labs from Q1 2021 - Q2 2022 ($ in millions)[1]

	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	Cumulative net income (loss) Q1 2021 - Q2 2022
		-$176.91	-$166.94	-$220.61	-$180.94	-$166.06	-$942.62
		$79.81	$122.52	$104.34	$153.98	$11.10	$672.44
		-$97.58	-$107.43	-$72.31	-$123.23	-$229.43	-$737.33
		$133.79	-$198.18	-$205.12	-$181.86	-$2,523.46	-$3,084.33
		-$4.70	$24.60	-$7.60	-$20.50	-$14.10	-$61.80
		-$116.00	-$151.30	-$40.60	-$138.60	-$145.15	-$655.55
		-$46.16	$32.73	-$40.19	-$76.90	-$85.74	-$408.04
		-$227.75	**-$444.00**	**-$482.10**	**-$568.05**	**-$3,152.84**	**-$5,217.23**

filings.

n of goodwill of $2.3 billion.

Understanding the unit economics of genetic testing labs

Beyond handwaving explanations why labs are unprofitable — and what it means for the clinical genomics workforce

CHRISTINA REN, MS, CGC
NOV 7, 2022

Article Highlights

- Recent hype in the sequencing market driven by product announcements from companies like Illumina ILMN -5.07%↓ and PacBio PACB -5.52%↓ overshadows the more sobering reality of layoff sprees and belt-tightening within genetic testing labs.
- This has caused many on the frontlines of clinical genomics to question the financial sustainability of unprofitable commercial labs and its impact on patient care.
- Reimbursement hell, capital-intensive tech stacks, race-to-the-bottom pricing, and broken economics of diagnostics development all make genetic testing a difficult line of business. It's no wonder why many are struggling, especially in the current macroenvironment.
- Most genetic testing labs are unprofitable today, but what ultimately matters is if a company can prove equity-efficient growth and a feasible road to future profitability.
- Amidst the pain, it's critical to recognize genetic counselors are the backbone of the genomic ecosystem for patients and providers. Medicare reimbursement and technology solutions are needed to deliver genetic services at scale.

#3: Lack of coverage by payors

- Securing payor coverage for expanded carrier screening (ECS) remains a challenge
- CPT code 81443 has not been covered by most insurance plans
  - Result is labs “stacking” CPT codes
- Uptick in denials has been observed, affecting lab reimbursement
- Some labs have promised patients low out-of-pocket costs when insurance does not cover testing

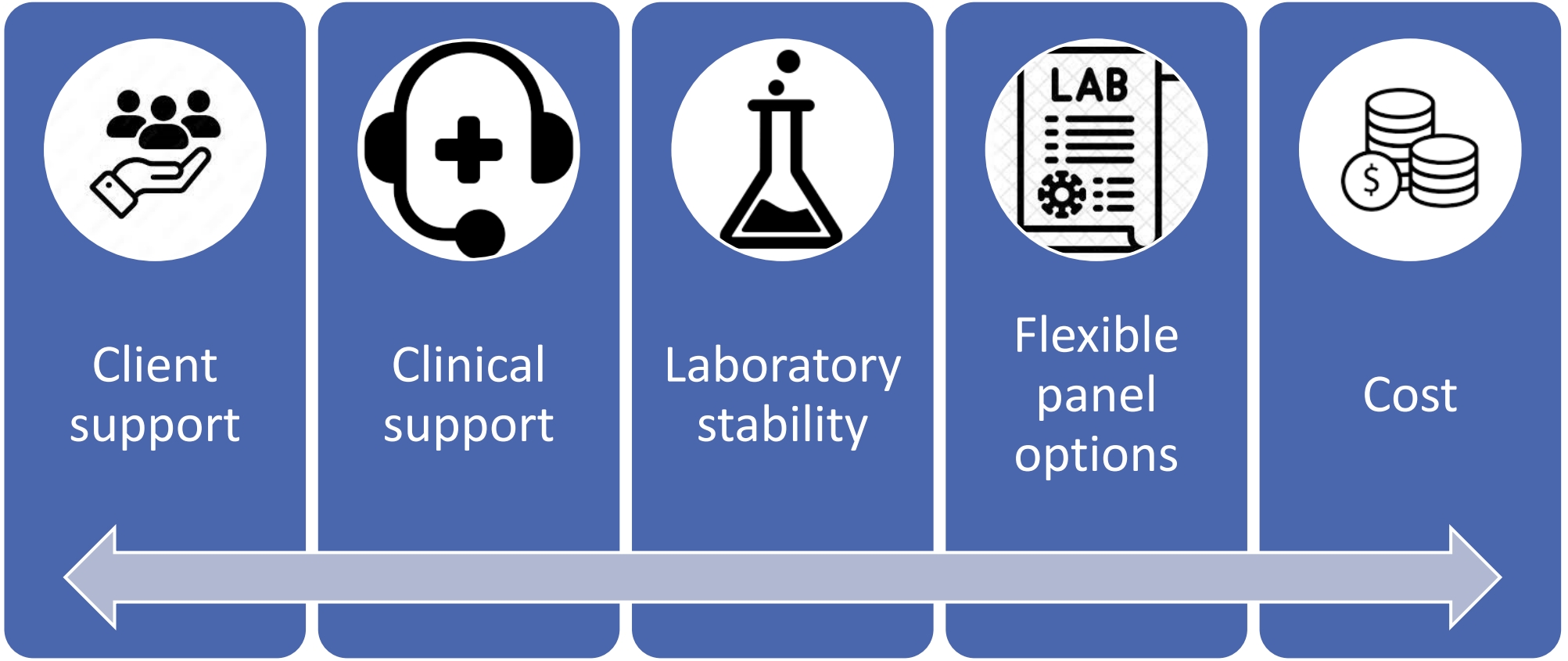
UnitedHealthcare Clamping Down on Expanded Carrier Screening, Genetic Counselors, Testing Firms Say

Feb 27, 2023 | Adam Bonislawski

Components of a successful carrier screening protocol

1) Vet your laboratory partner
2) Evaluate panel composition, size, and reporting policies
3) Consider use of gamete donation in the equation

1. Vetting your laboratory



Vetting your laboratory: Client support

Client support

- Integration with clinic logistics/EMR
- User-friendly portal
- Reasonable turn-around times
- Reliable support through local rep/client services
- Adaptability to feedback

Vetting your laboratory: Clinical support

Clinical support

- Access to clinical professionals
- Availability of genetic counseling services
- Transparency in testing/reporting policies
- Ability to tailor testing/reporting to client needs

Vetting your laboratory: Cost

- In-network status with payors
- Transparent, responsible billing practices
- Out of pocket options for patients?

Vetting your laboratory: Laboratory stability

Laboratory stability

- Profitability/losses
- Market share
- Diversity of testing portfolio (additional services outside reproductive genetics?)
- Scalability

Vetting your laboratory: Flexible panels

Flexible panel options

- Availability of guidelines-based panels
- Availability of custom panels
- Availability of single gene panels
- Inclusion/exclusion of benign conditions and variants

2. Evaluate panels and reporting

- ✓ Does the lab offer panels that meet/exceed professional guidelines?
- ✓ Does the lab offer flexibility and customization of their panels?
- ✓ Does the lab offer single gene testing options?
- ✓ Does the lab consider **technical difficulties for more common conditions** over adding **rare genes** with limited ability to interpret variants?
  - ✓Example: 21-hydroxylase deficient congenital adrenal hyperplasia
  - ✓Gene is difficult to test, but incidence (non-classic) is as high as 1 in 27 in some populations
- ✓ Does the lab practice quality, responsible reporting?

What results in reporting variability?

Laboratory policies

- Reporting benign variants
- Variant reclassifications
- Call out of “manifesting carriers”

Structure of test report

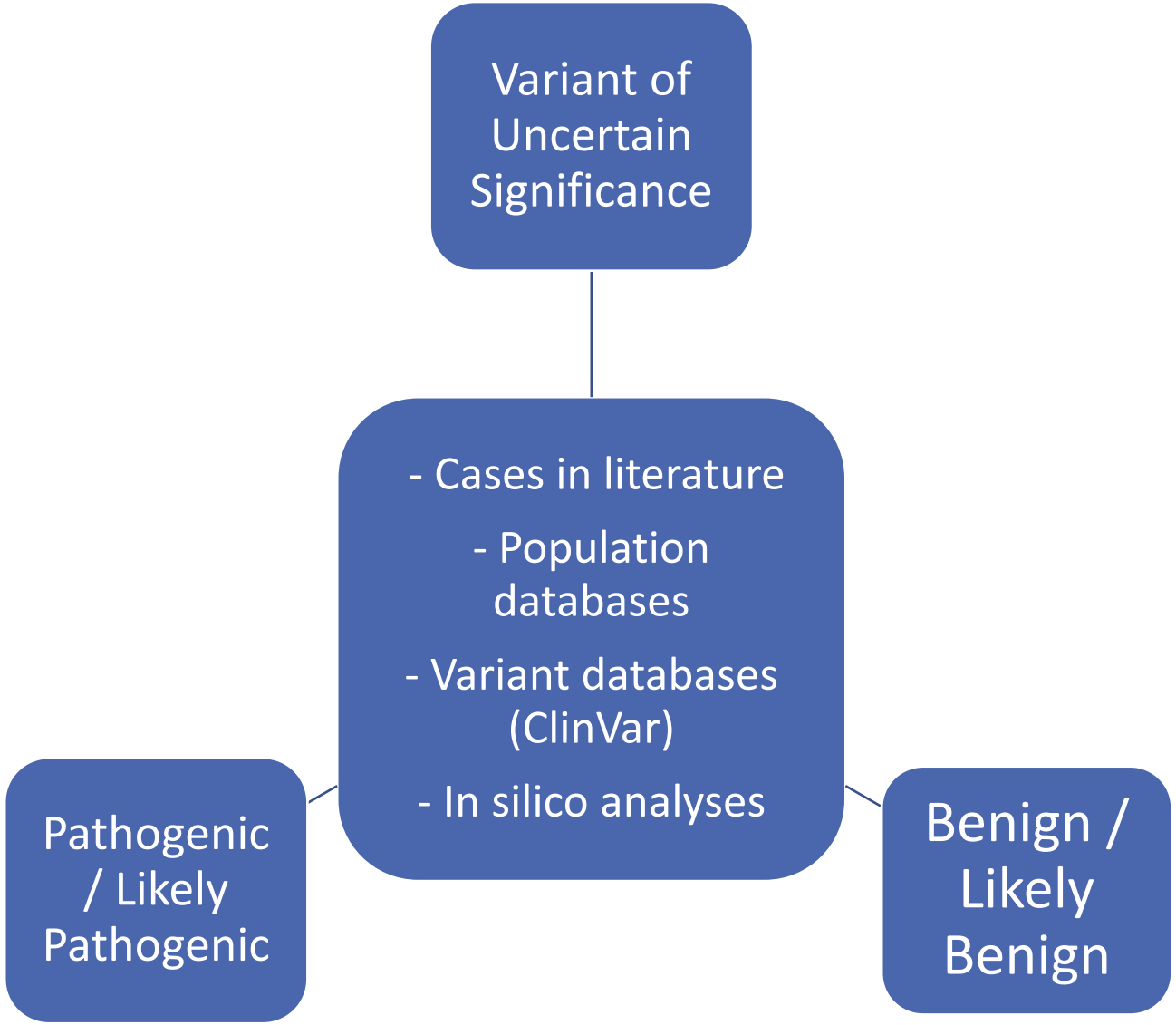
- Readability for non-genetics professionals
- Reportable as carrier or included under “special notes” / appendix section

Variant classification discrepancies

- Differing variant curation approaches
- Variable internal data

Detection rate/coverage

- Test methodology
- Testing of technically complex genes (*CYP21A2, F8, FXN*)


Variant of Uncertain Significance
- Cases in literature
- Population databases
- Variant databases (ClinVar)
- In silico analyses
Pathogenic / Likely Pathogenic
Benign / Likely Benign

Case example: Discrepant classifications

- Donor had prior genetic testing indicating he was a carrier for the c.886A>T variant in *GLA* associated with Fabry disease carrier status
- Lab closures/changes in testing logistics necessitated subsequent carrier screening at another laboratory
  - Carrier screening was negative for Fabry disease
- Second laboratory classified c.886A>T as VUS
  - Confirmed the lab was using the same evidence, but had different criteria for evidence of pathogenicity
- How to manage this donor's carrier status?

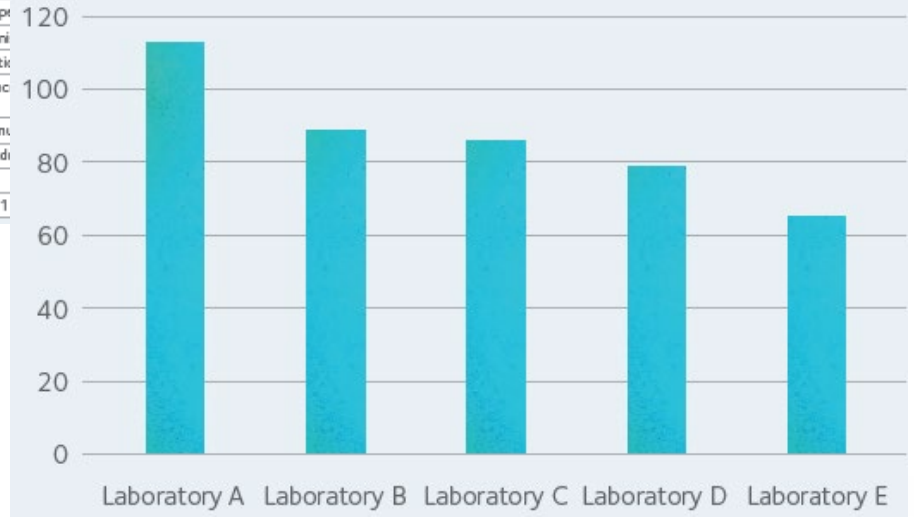
3. ECS & gamete donation

- Most new, prospective donors are having ECS during their qualification
- ECS is logistically more complex in third-party
- Ever-evolving panels and lab closures exacerbate difficulties with mismatched panels (Figure 1)
- Commercial ECS labs may not include certain genes on ACMG's Tier 3 list (Table 1)

Table 1: Tier 3 genes excluded from 4 out of 5 ECS panels

Gene Name	Condition Name	Inheritance Pattern
AFF2	Intellectual Development Disorder, X-linked 109 (AFF2)	X-linked recessive
ANO10	Spinocerebellar Ataxia, Autosomal Recessive 10 (ANO10)	Autosomal recessive
CCDC88C	Congenital Hydrocephalus 1 / Spinocerebellar Ataxia 40 (CCDC88C)	Autosomal recessive
CLCN1	Myotonia congenita (CLCN1)	Autosomal recessive
DYNC2H1	Short-rib Thoracic Dysplasia 3 with or without polydactyly (DYNC2H1)	Autosomal recessive
F8	Hemophilia A / Thrombophilia, X-Linked, due to Factor VIII Defect (F8)	X-linked recessive
FMO3	Trimethylaminuria (FMO3)	Autosomal recessive
FXN	Friedreich ataxia (FXN)	Autosomal recessive
GRIP1	Fraser syndrome 3 (GRIP1)	Autosomal recessive
LRP2	Donnai-Barrow syndrome (LRP2)	Autosomal recessive
MCPH1	Microcephaly 1, primary, autosomal rec	
MID1	Opitz GBBB Syndrome (MID1)	
MVK	Hyper-IGD syndrome / Mevalonic acid	
NAGA	Kanzaki disease / Schindler disease type	
OCA2	Albinism brown oculocutaneous / Albini	
PLP1	Pelizaeus-Merzbacher disease / Spastic	
RPGR	Cone-rod dystrophy, X-linked, 1 / Mac Retinitis pigmentosa (RPGR)	
SCO2	Mitochondrial complex IV deficiency, n	
SLC19A3	Thiamine metabolism dysfunction syndr	
TF	Atransferrinemia (TF)	
TNXB	Ehlers-Danlos syndrome, classic-like, 1	

FIGURE 1 Number of genes included from ACMG Tier 3 113 gene list



How do we evaluate clinical utility of ECS?

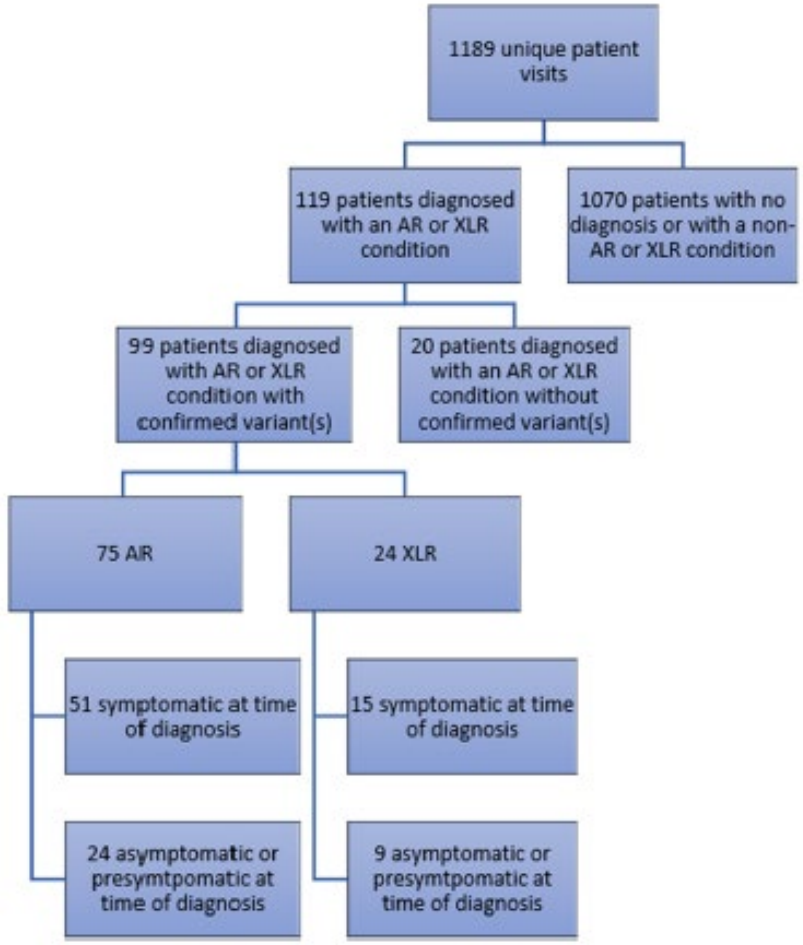
- ✓ Rate of carrier/carrier matches?
- ✓ Self-reported versus genetic ancestry?
- ✓ Frequency of carriers who would have been "missed" using ethnicity-based carrier screening?
- ✓ Reproductive decision-making in at-risk couples?
- ✓ Predictability of diagnoses of genetic conditions in a pediatric population?

Largely, there is **no consensus** as to the best way to approach this.

Examining pediatric populations

Pediatric clinic, academic institution

- Roche et al., 2023
- Retrospective chart review 2017 – 2020 of autosomal recessive (AR) & X-linked conditions
- 8% of patients were diagnosed
  - Of these, **61% could have been predicted** in advance using commercially-available 526 gene panel
- VUS cases were taken into account – these would not have been reported on ECS
- Most frequent diagnoses: G6PD deficiency, GJB2-related hearing loss, MCAD deficiency



Examining pediatric populations

Diagnosis	Gene involved	Did donor have ECS?	Gene on ACMG tier 3 list?
Child with 3-methylcrotonyl-CoA carboxylase deficiency	*MCCC1*	No	No
Child with congenital adrenal hyperplasia	*CYP21A2*	No	Yes
Child with congenital disorder of glycosylation type 1A	*PMM2*	No	Yes
Child with cystinosis	*CTNS*	No	No
Child with cystinosis	*CTNS*	No	No
Child with ectodermal dysplasia/odonto-onycho-dermal dysplasia	*WNT10A*	No	No
Child with Fraser syndrome	*FRAS1*	Yes	No
Child with Hurler syndrome	*IDUA*	No	Yes
Child with Joubert syndrome	*KIAA0586*	No	No
Child with MCAD deficiency	*ACADM*	No	Yes
Child with MCAD deficiency	*ACADM*	Yes	Yes
Child with mevalonate kinase deficiency	*MVK*	No	Yes
Child with nonketotic hyperglycinemia	*AMT*	No	No
Child with nonsyndromic hearing loss	*GJB2*	No	Yes
Child with nonsyndromic hearing loss	*STRC*	Yes	No
Child with nonsyndromic hearing loss	*GJB2*	No	Yes
Child with ocular myasthenia gravis	*POLG*	No	Yes
Child with phenylketonuria	*PAH*	No	Yes
Child with phenylketonuria	*PAH*	No	Yes
Child with phenylketonuria	*PAH*	No	Yes
Child with polycystic kidney disease	*PKHD1*	No	Yes
Child with Pompe disease	*GAA*	No	Yes
Child with Pompe disease	*GAA*	No	Yes
Child with Pompe disease	*GAA*	No	Yes
Child with primary microcephaly type 8	*CEP135*	Yes	No
Child with RYR1-related disease	*RYR1*	Yes	No
Child with Stargardt disease	*ABCA4*	No	No
Child with Usher syndrome type 2A	*USH2A*	Yes	Yes
Child with Usher syndrome type 2A	*USH2A*	No	Yes
Child with Usher syndrome type 2A	*USH2A*	No	Yes

DCP from gamete bank reports

- Isley et al., 2023
- Adverse outcome reports from three sperm banks from a three-year period were reviewed for diagnoses of AR conditions in donor-conceived persons (DCP)
- 30 cases were identified
  - 28 unique donors, 21 unique genes
  - **Five genes** (*PAH, GAA, GJB2, USH2A, ACADM*) were implicated in **more than one report** involving persons from different donors
- Taking VUS cases (n=6) into account, 43% of cases would have been predicted using an ACMG Tier 3 panel
  - ~80% of donors had undergone ethnicity-based screening only

Closing thoughts

- Addressed the massive upheaval in the reproductive genetics industry, resulting in major disruptions in the IVF space
- CALLS TO ACTION:
  - Acknowledge the need for genetic expertise in the reproductive medicine space
  - Support efforts related to recognition and reimbursement of genetic counseling as an independent service
- What does the future of carrier screening look like?
  - Is there a “one-size fits all” panel?
  - Will panels continue to get larger? Should they?
  - Will whole exome sequencing be the way of the future?

NEWS | CONSIDER THIS
April 27, 2023

Call for action amidst the turmoil of the reproductive genetics field

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