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Thesis Defense

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UAMS College of Health Professions

Arkansas Children's HOSPITALS · RESEARCH · FOUNDATION

How are genetic testing VUS results impacting pediatric case management within 6 months of results disclosure at a single institution?

Agenda

1. **Background**
2. **Study Aims**
3. **Methods**
4. **Results**
5. **Conclusions**

Definitions

- **Genetics Provider** – a provider that ordered genetic testing with a genetics background (e.g., geneticist or genetic counselor)
- **Non-Genetics Provider** – a provider that ordered genetic testing without a genetics background (e.g., cardiologist, neurologist, gastroenterologist, etc.)
- **Case/Case Encounter** – a provider encounter with patient at which time genetic testing was initially ordered

1. Background

How it all started...

- **Brayden West, MS, CGC**
- **Tiffany Lepard, MS, CGC**
- **Jing Jin, PhD**
- **Noelle Danylchuk, MS, CGC**

Committee

- Inclination towards the pediatric specialty
- Ambiguous genetic test result utility
- Psychology background → the resident devil's advocate

Personal Interests

Background

- For families searching for an etiology for their child's symptoms, the search for an answer can be an unpredictable and arduous journey.

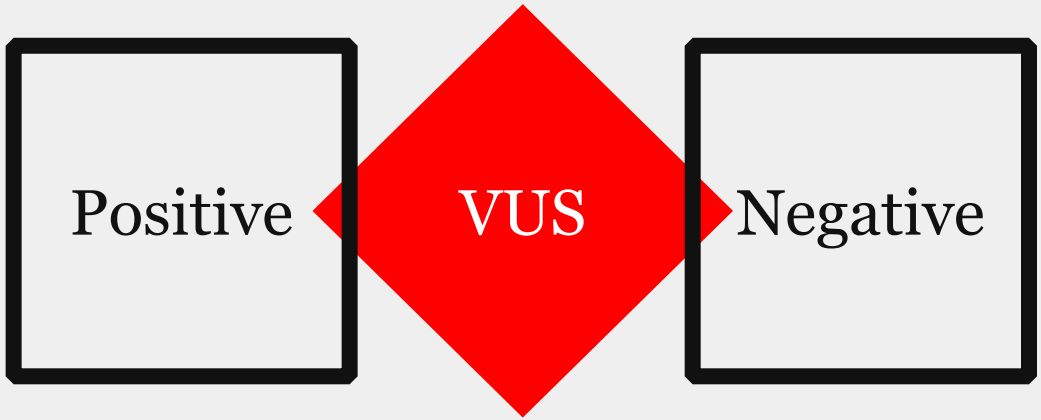
- Genetic testing may be a useful tool in aiding these families find answers.

Background Cont.

- Identifying disease-causing genetic changes and establishing a genetic diagnosis can guide pediatric case management and surveillance.

(Balasubramanian et al., 2019; Barsan et al., 2019; Ellapola et al., 2017; Manickam et al., 2021; Menke et al., 2021)

Genetic Testing Results



Classifying variants per ACMG

Incorporate clinical and population data

▼

Published guidelines for weighing evidence and classifying variants

▼

BUT

Background Cont.

- VUS results are common and occur more frequently with larger (more genes) testing panels (Shirts, Pritchard, & Walsh, 2016) .

- VUS results can complicate effective and efficient patient case management decisions (Burke et al., 2020).

Background Cont.

- A variant is classified as uncertain when there is not enough data to classify it as disease causing or not.
- The uncertainty of these variants indicates that they should not be used to aid in medical management decisions.

(Manickam et al., 2021; Nicolosi et al., 2022; Richards et al., 2015)

Background Cont.

- 26-40% of Non-Genetics providers felt ill-equipped to order and deliver test results to patients (Klitzmen et al., 2012).
- 74% of Non-Genetics providers rated their knowledge of genetics as very/somewhat poor and 87.1 % rated their knowledge of guidelines for testing similarly.
- However, most of these providers still ordered genetic testing for their patients.

Background Cont.

- Salm et al. (2013) conducted a similar study, looking at neurologist and psychologist perspectives on genetic testing utility.
- 47% of these Non-Genetics providers felt ill-equipped to order genetic tests, similar to Klitzmen et al.'s findings.
- In contrast to Klitzmen et al., 50% of these Non-Genetics providers rated their knowledge of genetics as having a moderate understanding.

(Klitzmen et al., 2012; Salm et al., 2013)

Background Cont.

- Scherr et al. (2020) found that different specialty providers in the cancer setting approached VUS follow-up management decisions differently.
  - Returning to clinic
  - Additional clinical exams
  - Expanded genetic testing

- Providers based their management decisions on various factors including the gene involved, psychosocial factors, the family history, and much more.

Background Cont.

- Makhnoon et al. (2021) conducted a similar study, but they also considered cancer-related surgery in the management assessment.
- In contrast, Makhnoon et al. (2021) found that there was no statistically significant difference in the follow-up medical management response to a VUS in the cancer setting.
- In fact, those with the VUS result received management similar to those with negative genetic test results.

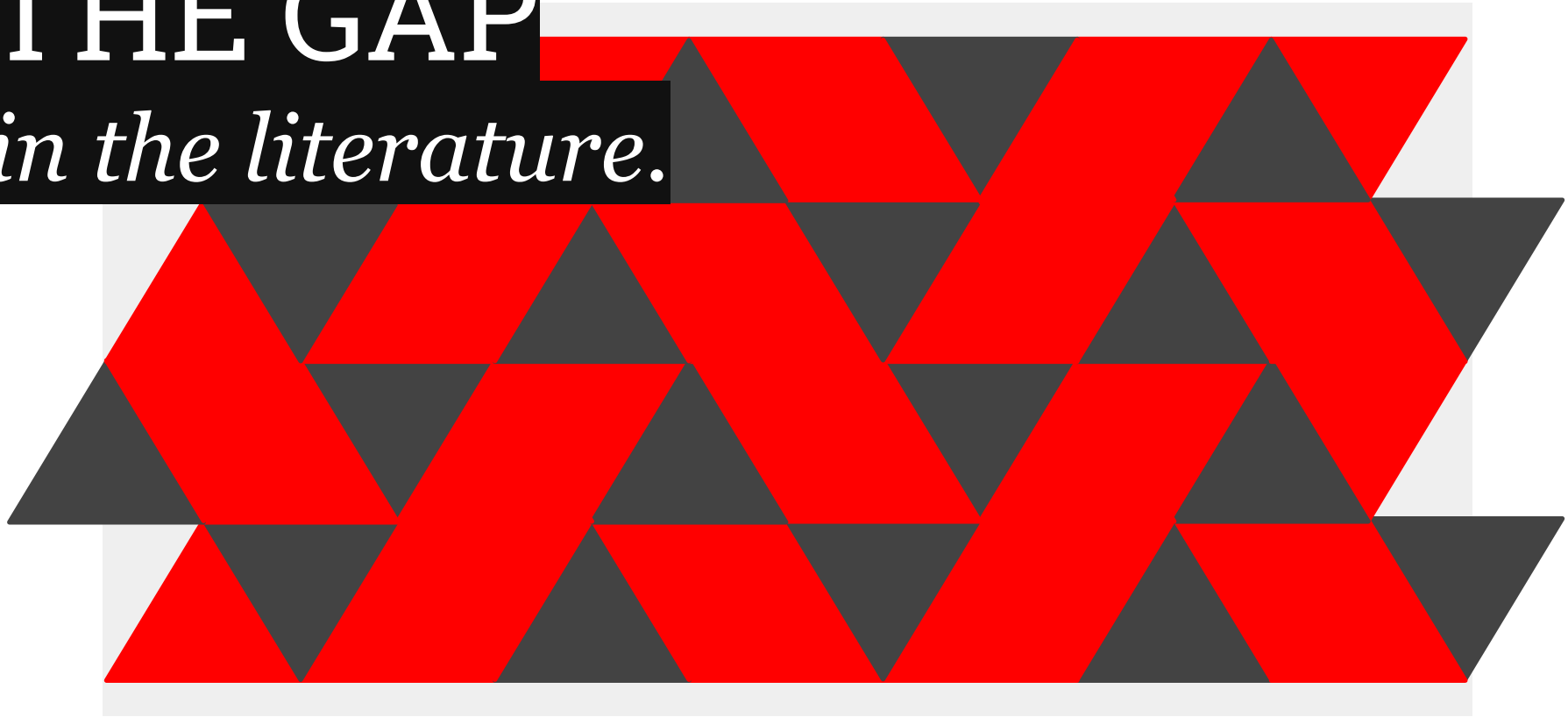
Background Cont.

- Menke et al. (2021) found that 67% of pediatric Non-Genetics providers incorrectly interpreted VUS results on a mock genetic test.
- Implying that pediatric Non-Genetics providers could be incorrectly interpreting VUS results in clinical settings.

Background Cont.

- Newey (2022) published a suggested framework for Non-Genetics providers to be mindful of VUS results when ordering genetic testing:
  - Awareness that larger gene panels have a higher potential of returning VUS results
  - Pretest counseling can be beneficial
  - Consider further analysis (e.g., familial testing, functional studies, etc.)
  - Multidisciplinary approach

THE GAP
in the literature.



The Gap

There remains limited information on the application of VUS results on pediatric patient management particularly across a wide range of pediatric specialties, not just genetics.

2. Study Aims

What we evaluated…

The Aims of the Study

- **Aim:** Assess the similarities and differences of various specialties as it relates to pediatric follow-up management within 6 months of genetic testing revealing a VUS result.
  - **Sub-aim 1:** Evaluate the type of genetic test ordered per provider group.
  - **Sub-aim 2:** Evaluate the follow-up plan per specialty.

3. Methods

How it was done...

Study Design

Who?

Patients with a VUS result, aged 0-21 years

What?

Restrospective chart review (n = 933)

Where?

Single pediatric institution

When?

Genetic testing

July 1, 2021 – March 31, 2023

UAMS IRB Approval # 275525

Testing Types

Whole exome sequencing

Targeted gene panel

SNP microarray

Karyotype testing

Single gene testing

Methylation study

Targeted familial testing

Identifying Cases

- Molecular Pathology Laboratory maintains an Excel database for genetic test utilization management and tracking ordered test data and results.

- Patients who had received a VUS result from genetic testing during the dates of interest were identified.
  - Patient medical record numbers (MRNs)
  - Gene name
  - Type of genetic test ordered
  - Which provider specialty ordered the test

Information Extracted from the EMR

A curated data collection sheet was created for this study to collect the desired information from a review of the electronic medical record base.

Information Extracted from the EMR

Table 1

Information Retrieved from the Electronic Medical Record

Main Components	Additional Components
Patient MRN	
Patient age at time of testing	<1 – 21 years
ICD-10 codes	
Ordering provider's medical specialty	
Genetic test ordered	Test code/ID (available on the order or preauthorization request)
The number of VUS results reported by the laboratory	Reported gene(s) name(s)
The delivery method of the genetic test result by the ordering provider	

Information Extracted from the EMR

Table 1

Information Retrieved from the Electronic Medical Record

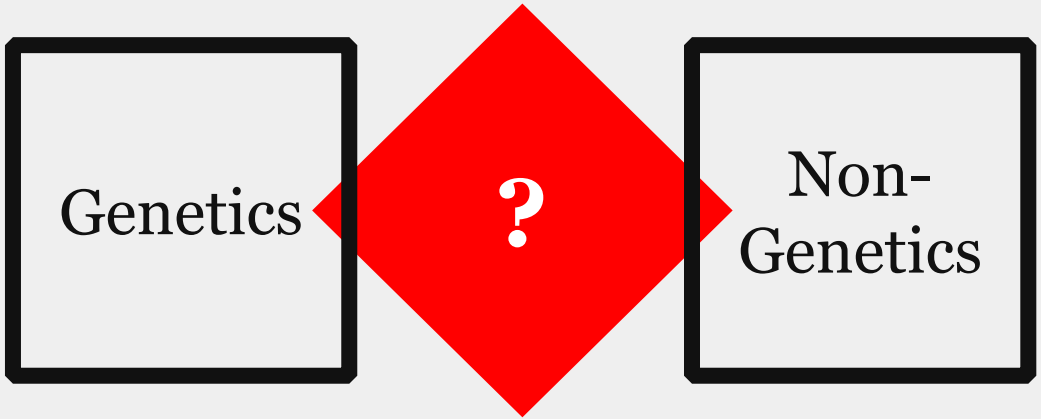
Main Components	Additional Components
Key information addressing each of the following management elements	Follow-up with the ordering provider (in person or telehealth). [Yes / No; If yes, how long before the follow-up consultation? (number of weeks, months, or years)]
	Testing of family members [Yes / No; If yes, who? (e.g., parents, siblings, etc.)]
	Additional genetic testing (Yes / No: If yes, what was recommended/ordered?
	Referral to other specialties (Yes / No: If yes, which specialists?)
	Imaging orders (Yes / No: If Yes, what was ordered?)
	Add-on laboratory orders (Yes / No: If yes, what was ordered?)
	Provider-to-provider consultation (Yes / No: If yes, which specialty?)

Information Extracted from the EMR

- Each MRN was assigned a study ID number.
- Upon completion of data collection:
  - Duplicate cases were removed
  - MRNs were removed from the curated data collection sheet, and only the study ID number was used to identify each case to ensure minimal risk to patients during data analyses.

Data Analysis

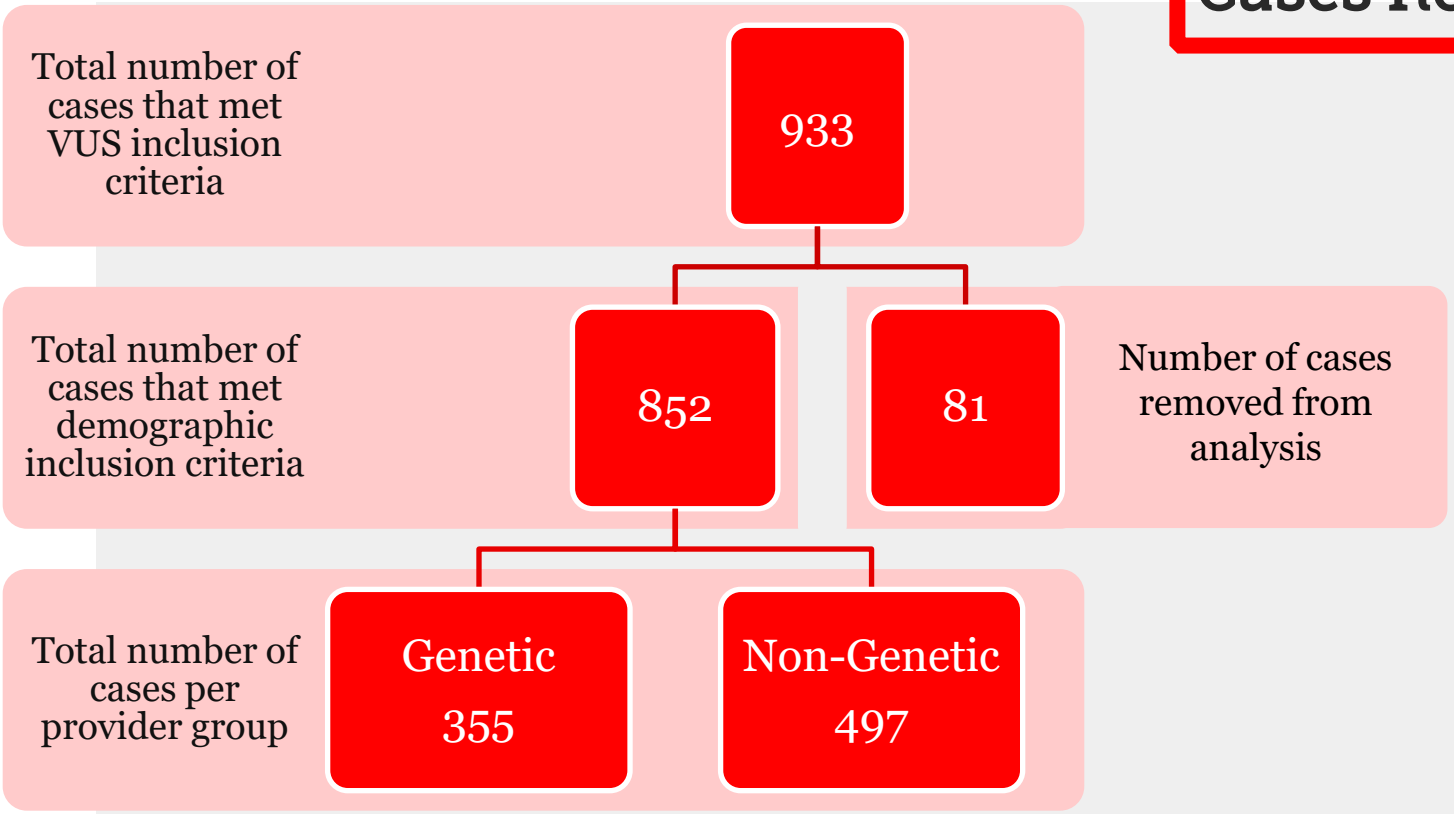
- Quantitative
- SPSS
- Direct comparison of two provider groups



4. Results

The collected data and analysis...

Cases Reviewed



Results

Table 2. Cases for inclusion ($N = 852$)

	Ordering Provider	
Characteristics	Genetics	Non-Genetics
n =	355	497
Age at time of testing		
0 – 11 months*	57	72
1 – 5 years	131	149
6 – 21 years	167	276
Average age of patient at time of testing (years)	6.4	7.3

Results

Table 2. Cases for inclusion (*N* = 852)

Characteristics	Ordering Provider: Genetics	Ordering Provider: Non-Genetics
n =	355	497
	n (%)	*n* (%)
Type of Testing Ordered		
WES		
Proband only	20 (6)	8 (2)
Duo/trio/quad	87 (25)	16 (3)
Reanalysis	6 (2)	2 (<1)
Targeted panel		
Proband only	145 (40)	444 (89)
Duo/trio/quad	79 (22)	26 (5)
SNP array	1 (<1)	0 (0)
Karyotype	0 (0)	0 (0)
Single gene	6 (2)	1 (<1)
Methylation study	0 (0)	0 (0)
Targeted Familial Testing	11 (3)	0 (0)

Note. $p < .001$ by Pearson's Chi-square test. WES = Whole Exome Sequencing.

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Table 3. Encounter completion ($N = 852$)

Characteristics	Ordering Provider	
	Genetics	Non-Genetics
n =	355	497
	n (%)	*n* (%)
Encounter type		
Completed encounter	340 (96)	351 (71)
Disclosure of results not documented in EMR	7 (2)	120 (24)
Patient lost to follow-up	8 (2)	26 (5)

Note. $p < .001$ by Pearson's Chi-square test. EMR = electronic medical record.

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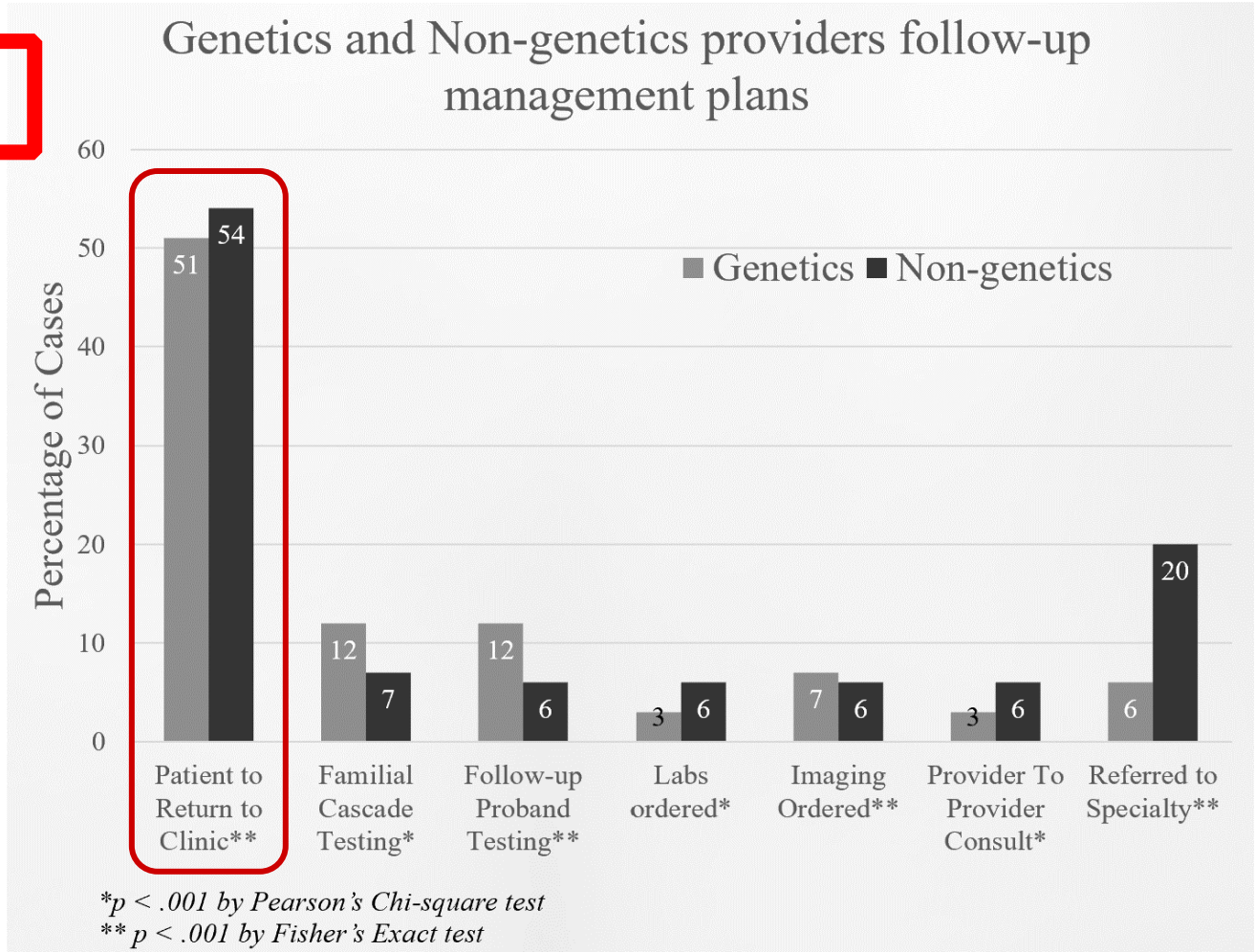
Genetics and Non-genetics providers follow-up management plans
Percentage of Cases
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Patient to Return to Clinic**
Familial Cascade Testing*
Follow-up Proband Testing**
Labs ordered*
Imaging Ordered**
Provider To Provider Consult*
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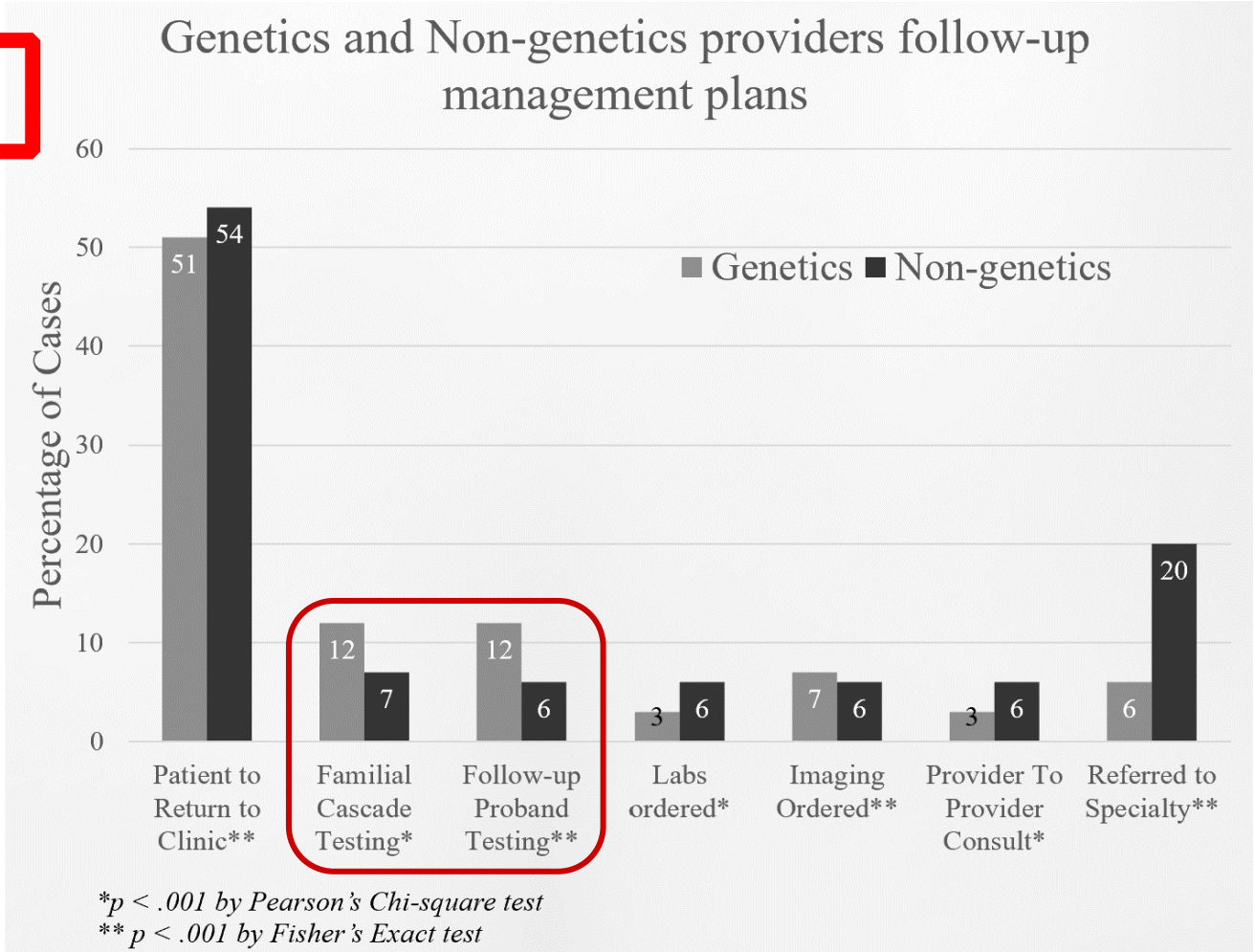
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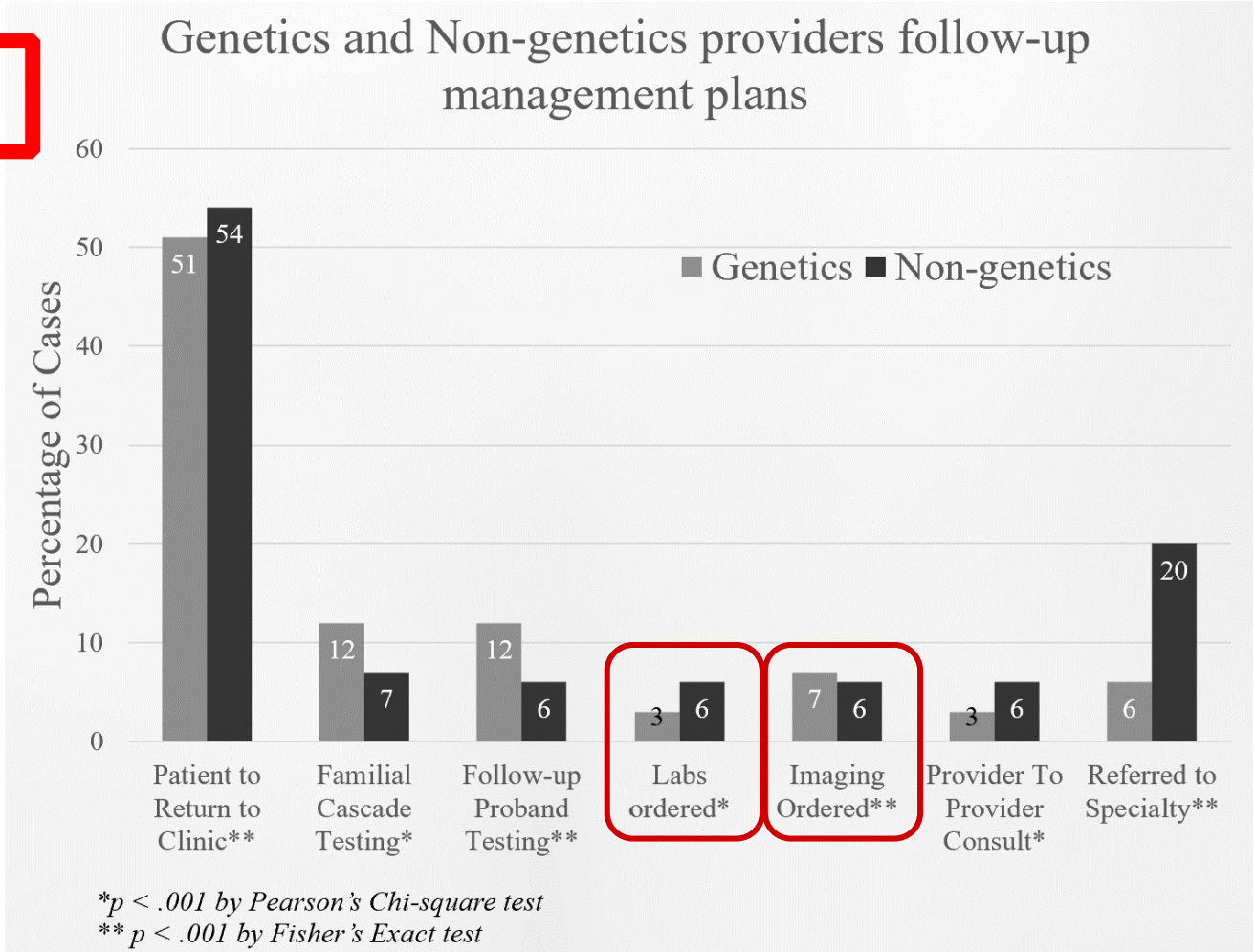
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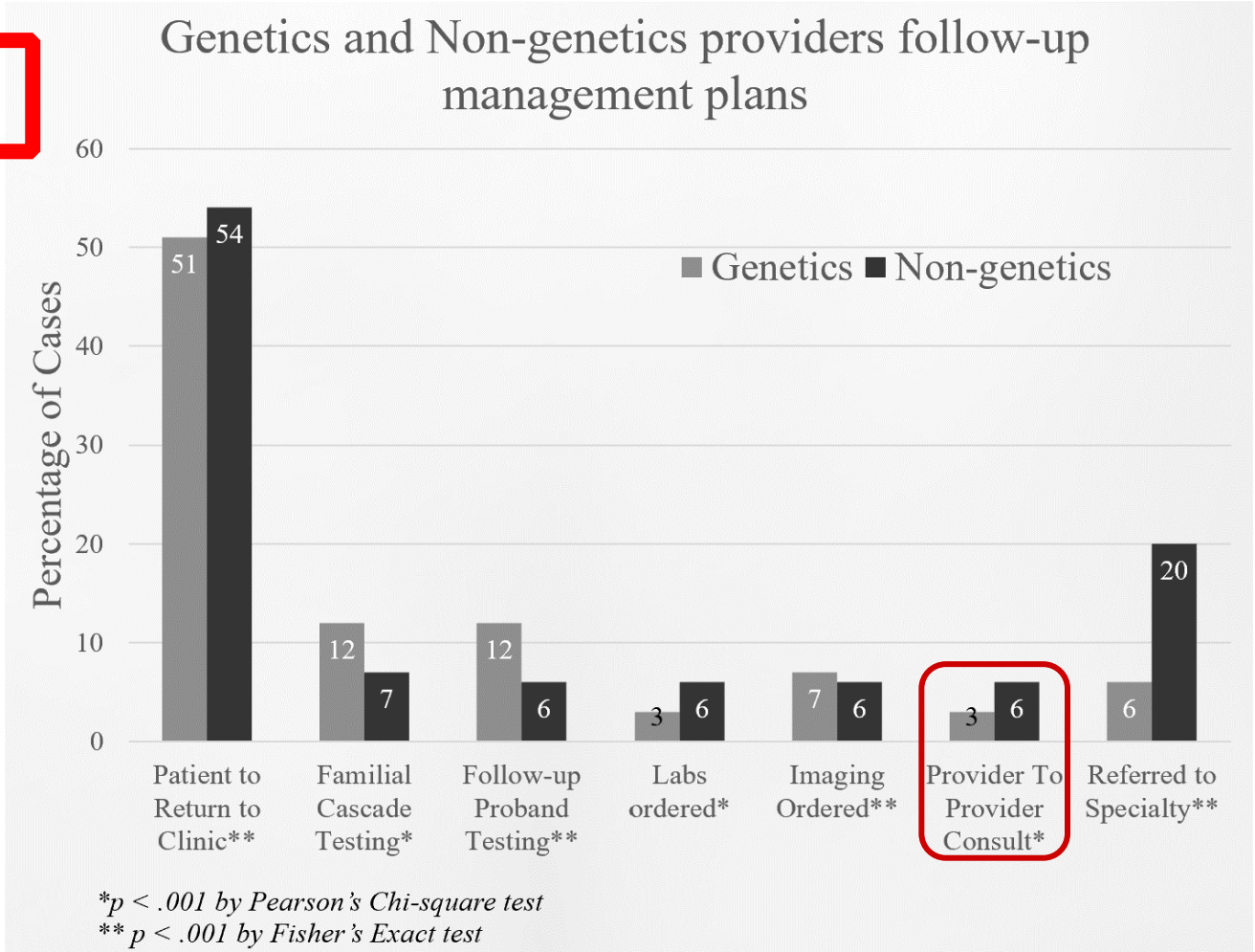
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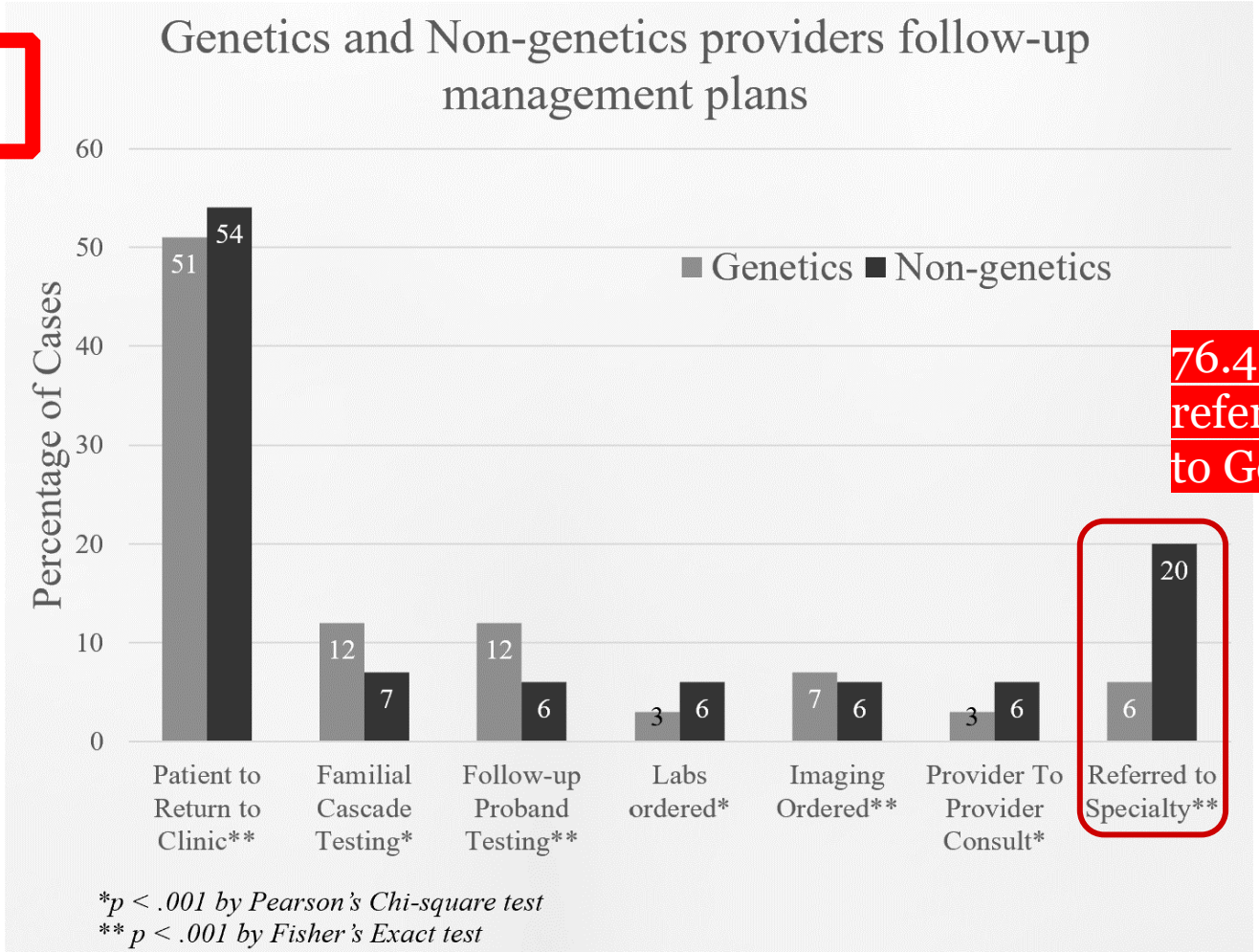

76.4% of the referrals were to Genetics

5. Conclusions

Let's talk about it

Conclusions: Evaluating genetic tests ordered

- Non-Genetics providers received 89% of VUS cases from proband-only targeted gene panels.
- Not including family samples could explain why more VUS cases came from Non-Genetics providers in this study group.
- This provider group could be ordering targeted panels that are indication and specialty specific.

Conclusions: Evaluating genetic tests ordered

- In contrast to Non-Genetics providers receiving most of their VUS results from targeted panels, our study revealed that Genetics providers were receiving VUS results from a variety of genetic tests.

- This is not surprising since genetic providers would be expected to order a wider array of genetic testing options and VUS results are possible from many types of tests.

Conclusions: Evaluating genetic tests ordered

- Genetics providers were also more likely to order genetic testing that initially included another family member's sample.
  - Tailored education on the utility of including family member samples

- All of a patient's clinical symptoms should be reported for more accurate interpretation of variants (Joynt et al., 2022; Richards et al., 2015).
- Including parental or family samples can aid in variant interpretation (Joynt et al., 2022; Richards et al., 2015).

Follow-up Management Differences

We found statistically significant differences in the types of follow-up management plans for cases that received a VUS result between Genetics and Non-Genetics providers.

Conclusions: Evaluating Follow-up Management

- In our study, there was statistical significance in how often providers disclosed VUS results and communicated a follow-up plan.
- Genetics providers more often disclosed and communicated a plan to patients within 6 months of testing than Non-Genetics providers.
- There could be a difference between the two provider groups in disclosure documentation or timelines.

Conclusions: Evaluating Follow-up Management

- There was also a statistical significance in how often patients were lost to follow-up with the provider after attempts to disclose VUS results.

- Non-Genetics providers had more patients lost to follow-up than Genetics providers.

Conclusions: Evaluating Follow-up Management

- The difference in patient loss to follow-up could be explained by the personal utility each patient holds in pursuing genetic testing.

- A previous study explored providers' perspectives of why a patient may not stay in touch to which it was primarily thought to be psychosocial – "limited understanding, interest, or motivation, perceived risk and anxiety, or other emotional response to the VUS" (Scherr et al., 2020, p. 664).

Conclusions: Evaluating Follow-up Management

- Previous studies have investigated the importance of:
  - Not solely using VUS results to aid in medical management decisions for patients (Manickam et al., 2021; Nicolosi et al., 2022; Richards et al., 2015).
  - Potential misinterpretation of VUS results by Non-Genetics providers (Menke et al., 2021).

Conclusions: Evaluating Follow-up Management

- Non-Genetics providers more often requested patients to return to clinic than Genetics providers.
- This was a similar finding to previous studies (Scherr et al., 2020) in which providers emphasized the importance of patient recontact to ensure patients have the opportunity to get future updates.

Conclusions: Evaluating Follow-up Management

- Genetics providers were more often pursuing familial cascade testing or follow-up testing for the proband.
- This could be an effort to further clarify VUS results, and providers have previously reported that further testing can be helpful (Scherr et al., 2020)
- Non-Genetics providers within this study may not have the background knowledge or available information to pursue this route of genetic test result clarification.

Conclusions: Evaluating Follow-up Management

- There was a difference between follow-up labs and imaging ordered between the two provider groups, however this was the least performed follow-up plan for both groups.
- The difference could be explained by the gene involved in the VUS case or clinical indications of the patient.
- Providers have explained that the gene involved can inform their decision to pursue additional labs and imaging, but this option was not often pursued (Scherr et al., 2020) which was also evident in our study.

Conclusions: Evaluating Follow-up Management

- Non-Genetics providers were more frequently referring patients to other provider specialties.
- This could be so that patients had an opportunity to undergo further evaluation of testing indications or referred to Genetics providers to aid in VUS clarification.
- Patients may also be seeking more information after receiving VUS results and requesting involvement with other specialties, which has been reported previously (Scherr et al., 2020).

Conclusions: Evaluating Follow-up Management

- Non-Genetics providers were referring patients to Genetics 76.4% of the time.

- Referring patients to a Genetics provider has been encouraged by previous research studies giving patients a point of contact for any testing related questions or additional counseling needs (Joynt et al., 2022; Newey, 2022).

Limitations

- Single institution
- Limited to pediatrics
- Total number of tests ordered by each provider group*

Future Directions

- Broader but similar study at multiple pediatric institutions
- Study the differences in specialty referral rates between Genetics and Non-Genetics providers more in depth.
- Further explore the differences in case management:
  - Other management steps taken
  - Comparing the differences across more specific specialties (e.g., neurology vs. genetics, cardiology vs. genetics, neurology vs. cardiology)

Final Thoughts

- Our study showed statistically significant differences between the two provider groups.
- Our data suggests that Genetics and Non-Genetics providers are approaching follow-up management differently in the pediatric setting.
- Previous studies have shown conflicting evidence of how patient management is impacted by VUS results in the cancer setting (Makhnoon et al., 2021; Scherr et al., 2020).

Final Thoughts

- Additional targeted education for Non-Genetics providers regarding VUS result utility may be beneficial.
  - Avoid unnecessary patient management
  - Improve a patient's diagnostic odyssey

- Provider education could include:
  - Importance of including family member samples
  - Limited utility of a VUS in a clinical setting
  - Restricted resources of Genetics providers to accommodate consultations for VUS results

The Importance

This study encapsulates the importance of understanding VUS result implications for this institution, and possibly similar institutions, potentially improving patient case management and hospital resource utilization.

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My fiancé

My mom and family


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Questions?