Communication Strategies in a Clinical Research Setting: What We Learned From eMERGE3

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National Academy of Science Workshop on Returning Genomic Results

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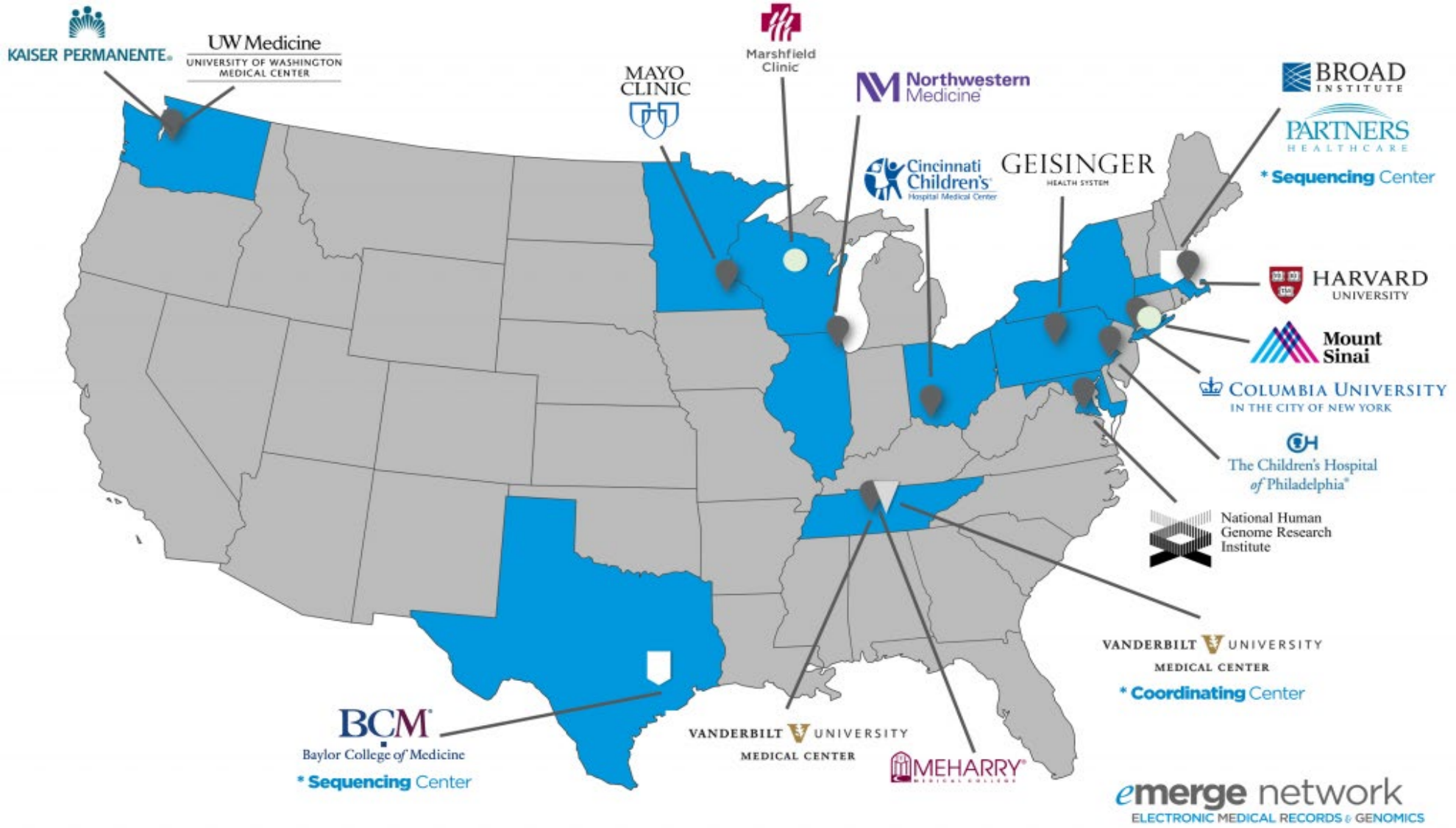
<u>Disclosures</u>
I am a section editor for *Genetics in Medicine*
I am a consulting cytogeneticist for Atlas Genomics

The Goal of eMERGE3: the intentional return of results (RoR) of clinically actionable variants to the consenting participants and their HCPs from a curated set of genes and to incorporate those results into the electronic health record



Methods for eMERGE3: Learning the Return of Results Process

- A questionnaire was developed with over 30 different parameters to determine the process of return of results (RoR) for each eMERGE3 site
- Interviews with clinicians at the 10 different clinical sites were conducted by Dr. Georgia Wiesner
- Each clinical site developed their own return of result process based on population recruited and institutional requirements; several sites had more than one process for return of results
- All return of result processes were approved by the local IRB

Variables in Design and Consent Process that Impacted RoR

- Whether a participant who was selected from biorepositories had consented for enrollment prior to or after their DNA sample were submitted to one of the two sequencing laboratories.
- Whether an individual who declined results disclosure would still be consider part of a site's cohort.
- Whether a site allowed other opportunities for a participant to opt-out of results disclosure
- Methods used for the disclosure of results to participants and whether that method required participant engagement. Methods used across clinical sites include an in-person appointment with medical geneticist/genetic counselor, phone call, mail, or notification via a portal. Some sites had multiple methods for results disclosure.

Essential Elements for RoR at All Sites

- Disclosure to Participant
- Informing the Healthcare Provider
- Uploading results to the Electronic Health Record

Participant Disclosure

Healthcare Provider Informed

Upload to the EHR

There is variability across sites for the order of essential elements in their RoR process

Site	1st Step	2nd Step	3rd Step
CHOP			
KPWA/UW			
MMC			
NU			
CCHMC			
HP			
MC			
VUMC			
CU			
GMS			

eMERGE3 Return of Results

- A total of 25,084 participants recruited from biorepositories and community organizations
- Of the 10 clinical sites, two were pediatric and eight were adult
- DNA sequencing performed at Partners HealthCare Laboratory for Molecular Medicine (LMM) and the Baylor College of Medicine Human Genome Sequencing Center (HGSC) Clinical Laboratory
- eMERGEseq platform had 109 genes and 1551 variants
  - **Genomic results returned to eMERGE3 participants were a consensus panel of 67 genes and 14 SNV's, including 58 of the 59 ACMG list of actionable genes**

All Clinical Sites Were Required to Return Pathogenic/Likely Pathogenic Variants

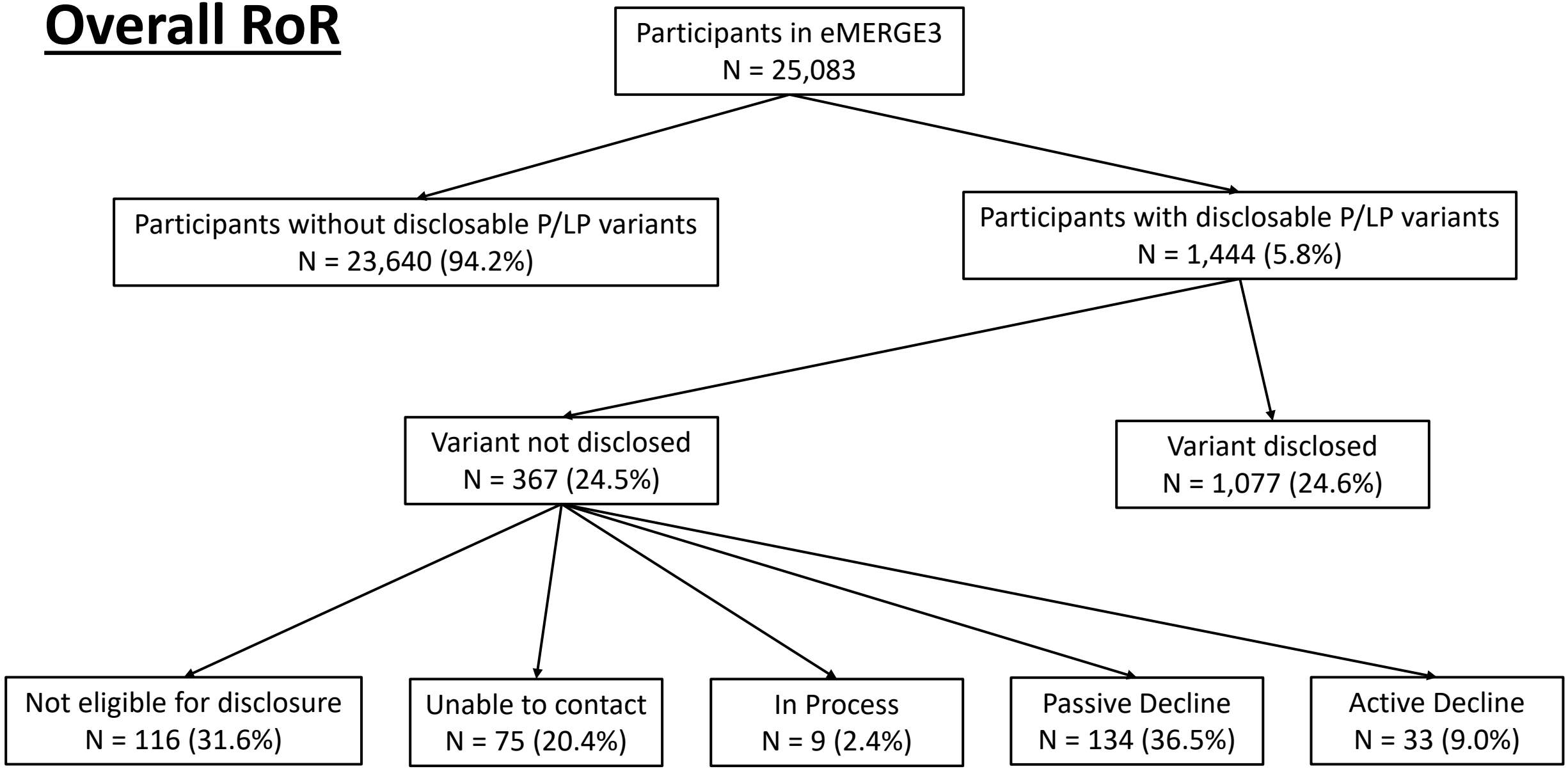
Type of Genomic Variant	Number of Clinical Sites Returning that Type of Variant
Pathogenic/Likely Pathogenic	10
Variants of Uncertain Significance	6
Recessive Gene ”Carrier” or Heterozygote	1
Pharmacogenetics	4
Null or negative results	6

- *Not all sites included genetic counseling in the return of P/LP Variants*

For the eMERGE3 analysis, results tabulated and tracked by the coordinating center and included:

- Number of participants with P/LP variants.
- Number of participants who completed disclosure of results for their P/LP.
- Number of participants that had genetic counseling as part of the disclosure of their P/LP variant.

Overall RoR


Participants in eMERGE3
N = 25,083
Participants without disclosable P/LP variants
N = 23,640 (94.2%)
Participants with disclosable P/LP variants
N = 1,444 (5.8%)
Variant not disclosed
N = 367 (24.5%)
Variant disclosed
N = 1,077 (24.6%)
Not eligible for disclosure
N = 116 (31.6%)
Unable to contact
N = 75 (20.4%)
In Process
N = 9 (2.4%)
Passive Decline
N = 134 (36.5%)
Active Decline
N = 33 (9.0%)

eMERGE3 Clinical Sites

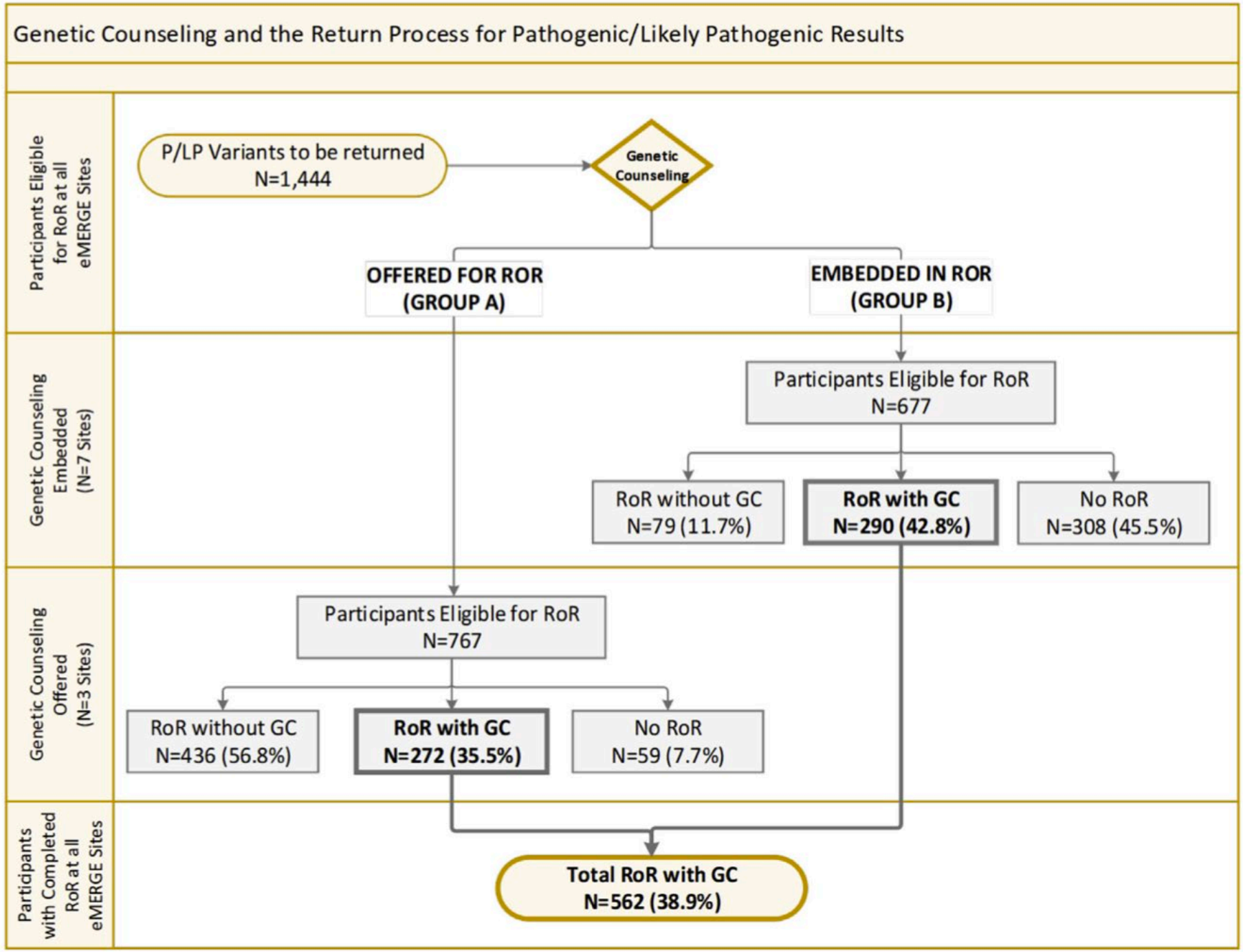
Institution	Total # Participants	# Participants with P/LP Variants	# Participants with Returned P/LP
CCHMC prospective adolescent	160	6 (3.8%)	5 (83.3%)
CCHMC biobank	2840	91 (3.2%)	19 (20.9%)
CHOP	2990	101 (3.4%)	24 (23.8%)
Columbia IMAgene	341	30 (8.8%)	28 (93.3%)
Columbia- prospective	1120	65 (5.8%)	51 (78.5%)
Columbia -retrospective	1135	73 (6.4%)	18 (24.7%)
Geisinger	2500	263 (10.5%)	244 (92.8%)
KPWA/UW	2500	96 (3.8%)	58 (60.4%)
Mayo - Rochester	2535	121 (4.8%)	118 (97.5%)
Mayo - Arizona	500	10 (2.0%)	9 (90.0%)
Meharry	500	19 (3.8%)	14 (73.7%)
Northwestern	3000	279 (9.3%)	255 (88.5%)
Partners Healthcare	2500	65 (2.6%)	25 (35.5%)
VUMC	2454	225(9.1%)	209 (92.8%)
Total	25,084	1444 (5.7%)	1077 (74.6%)

Summary of Findings:

- Disclosure of P/LP variants ranged from 23.7% to 94.9% across clinical sites
- The two pediatric institutions of CCHMC and CHOP had similarly low disclosure of approximately 24%
- Sites that had a consent process that required participants to either have their results disclosed or be excluded from the cohort were able to return more P/LP results
- Sites that recruited participants from a biorepository and consented participants after sample submission for sequencing were able to disclose fewer P/LP variants
- Sites where consented participants had the option to “opt-out” after sequencing had fewer participants that continued to result disclosure
- Sites that disclosed results by mail or unscheduled phone calls were more successful reaching participants than those who required participants to make an appointment, phone call or activate a portal for results disclosure

Genetic Counseling and RoR: Offered vs. Embedded

GROUP	Institution	Age Group	Source of Participants	Return of Results Required for Enrollment	Primary Planned Method for RoR	Genetic Counseling with RoR*
Group A	GE	Adult	Biorepository	Yes	Letter	Offered
	NU	Adult	Clinic, PGx Biorepository	Yes	Phone	Offered
	VUMC	Adult	Clinic, PGx Biorepository	Yes	Letter	Offered
Group B	CU	Adult	Community Clinic, Biorepository	No	Clinic, Portal, Letter, Email	Embedded
	KPWA/UW	Adult	Biorepository	No	Clinic	Embedded
	MC[1]	Adult	Biorepository	No	Clinic	Embedded
	MMC	Adult	Clinic	No	Clinic	Embedded
	PHC	Adult	Biorepository	No	Clinic	Embedded
	CCHMC	Pediatric	Biorepository, Clinic, Community	No	Clinic, Portal	Embedded
	CHOP	Pediatric	Biorepository	No	Clinic	Embedded


Genetic Counseling and the Return Process for Pathogenic/Likely Pathogenic Results
Participants Eligible for RoR at all eMERGE Sites
P/LP Variants to be returned N=1,444
Genetic Counseling
OFFERED FOR ROR (GROUP A)
EMBEDDED IN ROR (GROUP B)
Genetic Counseling Embedded (N=7 Sites)
Participants Eligible for RoR N=677
RoR without GC N=79 (11.7%)
RoR with GC N=290 (42.8%)
No RoR N=308 (45.5%)
Genetic Counseling Offered (N=3 Sites)
Participants Eligible for RoR N=767
RoR without GC N=436 (56.8%)
RoR with GC N=272 (35.5%)
No RoR N=59 (7.7%)
Participants with Completed RoR at all eMERGE Sites
Total RoR with GC N=562 (38.9%)

RoR and Genetic Counseling

	Group A: Clinical Sites offering Genetic Counseling in the RoR Process	Group B: Clinical Sites with Genetic Counseling embedded in the RoR Process	All Clinical sites
Total Participants with P/LP Variants	767	677	1,444
Total Participants with P/LP Variants Returned	708 (92.3%)	369 (54.5%)	1,077 (74.5%)
Total Participants with P/LP Variants Returned and Genetic Counseling	272 (38.4%)	290 (78.6%)	562(38.8%)

Genetic Counseling and RoR: Group A (Offered) 38.4% vs. Group B (Embedded) 78.6%, $P = .0052$
Total Disclosure: Group A (GC Offered) 92.3% vs. Group B (GC Embedded) 54.5%, $P = .00001$

eMERGE3: A Ten-Armed Real-Life Experiment in Genomic Medicine

Common Themes Observed in Design Elements that Influence RoR

- Timing of the recruitment and consent process, relative to DNA sample submission for sequencing was important, particularly from biorepositories
- Sites where consented participants were required to have disclosure of results for enrollment had a higher number of participants who had completed results disclosure
- Sites that include “opt-out” opportunities had fewer consented participants complete result disclosure
- Sites that required genetic counseling as part of their disclosure returned fewer results
- Methods for result disclosure that require participant engagement were less successful for disclosing results

Participant Engagement

- What factors influenced engagement of participants through the course of a research study?
- What are the genetic counseling needs for participants engaging in genomic medicine research?
- How do we best provide genetic counseling to our participants? Is the traditional in-person or phone visit the only way to support participants?

Genetics inMedicine

www.nature.com/gim

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BRIEF COMMUNICATION

Preferences of biobank participants for receiving actionable genomic test results: results of a recontacting study

Nora B. Henrikson[1]✉, Aaron Scrol[1], Kathleen A. Leppig[1], James D. Ralston[1], Eric B. Larson[1] and Gail P. Jarvik[2]

KPWA/UW eMERGE3 cohort

- Recruited from a biobank
- Recontacted 123 participants
- 87 participants responded (70.7%)
- 62 of these 87 participants declined the offer for RoR (71.3%)
- Most common reason for declining results were not wanting to know (n =22) and concerns about insurability (n =28)

Unknowns

- How many participants received genetic counseling outside of the planned disclosure process?
- Whether participants who had results disclosed by mail always opened the mail?
- Whether the participants who received their results outside of traditional genetic counseling session understood the significance of P/LP variant?
- Although outside the scope of eMERGE3, how frequently relatives at risk had the opportunity for cascade testing?
- Are their better methods for providing genetic counseling when disclosing genomic results obtained during a research study?

Reanalysis of Variants

Genetics in Medicine (2022) 24, 454–462

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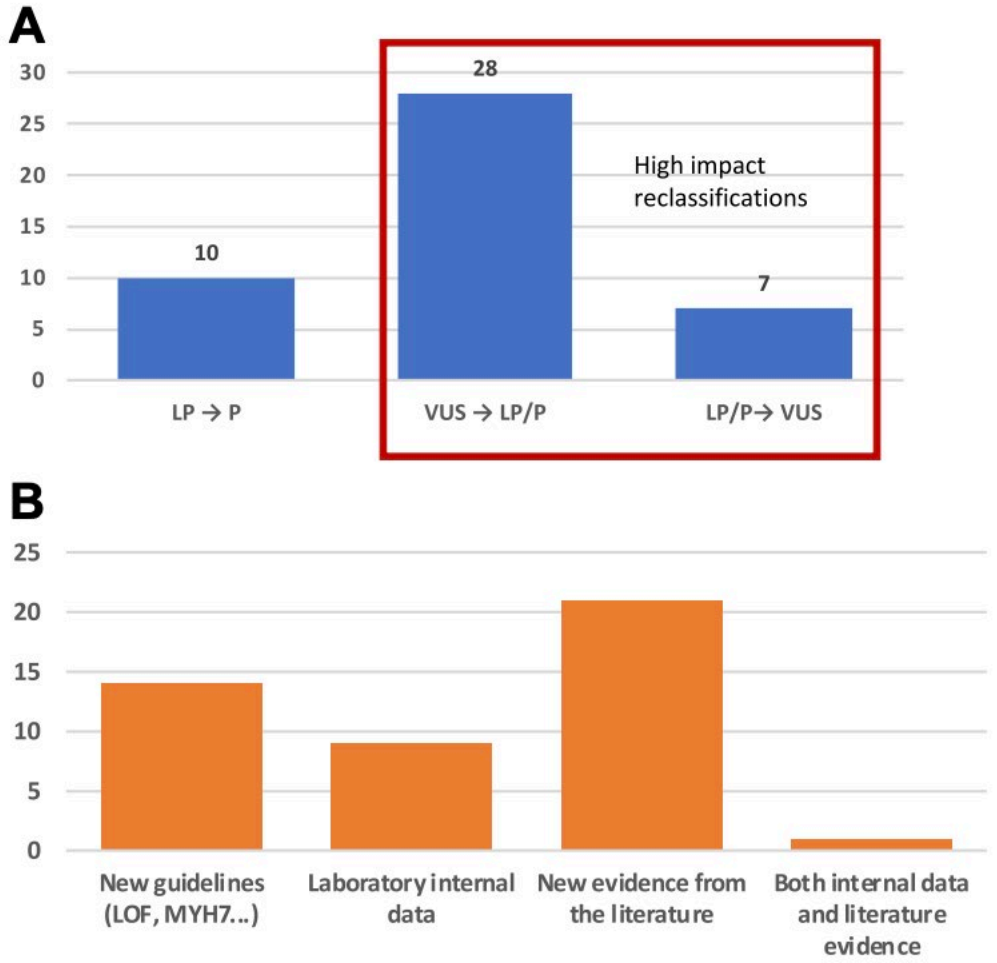
Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Reanalysis of eMERGE phase III sequence variants in 10,500 participants and infrastructure to support the automated return of knowledge updates

Hana Zouk[1,2], Wanfeng Yu[1], Andrea Oza[1], Megan Hawley[1], Prathik K. Vijay Kumar[1], Christopher Koch[1], Lisa M. Mahanta[1], John B. Harley[3,4,5], Gail P. Jarvik[6], Elizabeth W. Karlson[7], Kathleen A. Leppig[8], Melanie F. Myers[3,4], Cynthia A. Prows[3], Marc S. Williams[9], Scott T. Weiss[7], Matthew S. Lebo[1,7,10], Heidi L. Rehm[1,2,7,10,11,*]



The passage to safe harbor is marked by wrecked ships

OR

What would you do differently if you could redo eMERGE3?

Goal: to develop a toolbox of best practices for returning genomic results in research and clinical studies

Journal of *Personalized Medicine*

MDPI

Article

Returning Results in the Genomic Era: Initial Experiences of the eMERGE Network

Georgia L. Wiesner [1,*], Alanna Kulchak Rahm [2], Paul Appelbaum [3], Sharon Aufox [4], Sarah T. Bland [5], Carrie L. Blout [6], Kurt D. Christensen [7], Wendy K. Chung [8], Ellen Wright Clayton [9], Robert C. Green [10], Margaret H. Harr [11], Nora Henrikson [12], Christin Hoell [13], Ingrid A. Holm [14], Gail P. Jarvik [15], Iftikhar J. Kullo [16], Philip E. Lammers [17], Eric B. Larson [12], Noralane M. Lindor [18], Maddalena Marasa [19], Melanie F. Myers [20], Josh F. Peterson [21], Cynthia A. Prows [22], James D. Ralston [12], Hila Milo Rasouly [19], Richard R. Sharp [23], Maureen E. Smith [24], Sara L. Van Driest [25], Janet L. Williams [2], Marc S. Williams [2], Julia Wynn [26] and Kathleen A. Leppig [27]

Genetics in Medicine (2022) 24, 1130–1138

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Genetics in Medicine

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ARTICLE

The reckoning: The return of genomic results to 1444 participants across the eMERGE3 Network

Kathleen A. Leppig[1,*], Alanna Kulchak Rahm[2], Paul Appelbaum[3], Sharon Aufox[4], Sarah T. Bland[5], Adam Buchanan[2], Kurt D. Christensen[6], Wendy K. Chung[3], Ellen Wright Clayton[5], David Crosslin[7], Josh Denny[8], Shannon DeVange[1], Adam Gordon[4], Robert C. Green[5], Hakon Hakonarson[9], Margaret H. Harr[9], Nora Henrikson[10], Christin Hoell[4], Ingrid A. Holm[11], Iftikhar J. Kullo[12], Gail P. Jarvik[7], Philip E. Lammers[13], Eric B. Larson[10], Noralane M. Lindor[12], Maddalena Marasa[3], Melanie F. Myers[14], Emma Perez[6], Josh F. Peterson[5], Siddharth Pratap[15], Cynthia A. Prows[14], James D. Ralston[10], Hila Milo Rasouly[3], Dan M. Roden[5], Richard R. Sharp[12], Rajbir Singh[15], Gabriel Shaibi[16], Maureen E. Smith[4], Amy Sturm[2], Heidi A. Thiese[1], Sara L. Van Driest[4], Janet Williams[2], Marc S. Williams[2], Julia Wynn[3], Carrie L. Blout Zawatsky[6], Georgia L. Wiesner[5]

emerge network

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- Heidi Thiese

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- Noralae Lindor
- Gabriel Shaibi
- Richard Sharp

Meharry Medical Center

- Phil Lammers
- Rajbir Singh

Northwestern University

- Sharon Aufox
- Christin Hoell
- Adam Gordon
- Maureen Smith

Vanderbilt University Medical Center/Meharry

- Sarah Bland
- Ellen Wright Clayton
- Philip Lammers
- Josh Peterson
- Siddarth Pratap
- Dan Rodin
- Rajibar Singh
- Georgia Wiesner*

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