Return of Individual Research Results from Genome-Wide Association Studies:

The experience of the eMERGE Study

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on behalf of
the eMERGE
Return of Results
Oversight Committee

eMERGE – www.gwas.net

- electronic MEdical Records and GEnomics Research Consortium
  - Cooperative Agreement of 5 Partner Institutions: Group Health/University of Washington, Marshfield, Mayo, Northwestern, and Vanderbilt (eMERGE2 adds Geisinger and Mt. Sinai). NHGRI funded.
  - to develop, disseminate, and apply approaches that combine DNA biorepositories with electronic medical record (EMR) systems for large-scale, high-throughput genetic research
- Consent & Community Consultation Workgroup on Result Return
- Return of Results Oversight Committee

C&CC RoR Workgroup

- Kyle Brothers (Vanderbilt)
- Wylie Burke (UW)
- Ellen Clayton (Vanderbilt)
- Lynn Dressler (UNC Chapel Hill)
- **Malia Fullerton (UW, Chair)**
- Gail Jarvik (UW)
- Barbara Koenig (Mayo)
- Maureen Smith (Northwestern)
- Amy McGuire (Baylor)
- Carol Somkin (Kaiser Permanente)
- Holly Tabor (Seattle Children's)
- Sue Trinidad (UW)
- Carol Waudby (Marshfield)
- Ben Wilfond (Seattle Children's)
- Wendy Wolf (Northwestern)

eMERGE RoR Oversight Committee

Institution	Member	Clinical Training
GHC/UW	**Gail Jarvik (Chair)**	Med/MedGen
	Kathy Leppig	Peds/MedGen/Cyto
	Malia Fullerton	
Marshfield	Cathy McCarty	
	Marilyn Ritchie	
Mayo	Joan Henriksen Hellyer	
	Laney Lindor	FP/MedGen
Northwestern	Phil Greenland	Med/Cardiol
	Maureen Smith	Genetic Counseling
Vanderbilt	Kyle Brothers	Peds
	Ellen Clayton	Peds
	Dana Crawford	
Genotyping Ctrs	Daniel Mirel (Broad)	

Nature of expected findings

- Genome-wide Association Studies
  - Common variants
  - Many statistically significant findings
  - *Clinical* relevance of most findings low
  - BUT incidental findings also
- Easily Anticipated Future Findings
  - Copy Number Variation and similar
  - Rare clinically relevant variants identified by re-sequencing
  - eMERGE2 will employ a pharmacogenetic array

Institution	Biorepository Population	Ongoing Participant Contact	Current / Expected Size	Age Range / Mean Age	Consent for RoR?
Group Health Cooperative / University of Washington (Seattle, WA)	**Disease-specific:** Alzheimer's disease patient registry & Adult Changes in Thought Study	Yes	**~4,000** >96% Caucasian	65 – 90+ (74)	Yes
Marshfield Clinic (Marshfield, WI)	**Population:** Personalized Medicine Research Project	No	**20,000 / 21,000** 98% Caucasian	18 – 90+ (48)	No
Mayo Clinic (Rochester, MN)	**Disease specific:** Mayo Clinic Non-Invasive Vascular Laboratory	Yes	**750 ea. PAD & controls** >96% Caucasian	17 – 90+	Yes
Northwestern University (Chicago, IL)	**Population:** NUgene Project	No	**8,500 / 20,000** 12% AA 8% Hispanic	18 – 90+ (50)	No
Vanderbilt University (Nashville, TN)	**Population:** BioVU	No	**75,000+ / 200,000** 13% AA	18 – 90+ (52)	No De-id'd

Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group.

Fabsitz RR, McGuire A, Sharp RR, Puggal M, Beskow LM, Biesecker LG, Bookman E, Burke W, Burchard EG, Church G, Clayton EW, Eckfeldt JH, Fernandez CV, Fisher R, Fullerton SM, Gabriel S, Gachupin F, James C, Jarvik GP, Kittles R, Leib JR, O'Donnell C, O'Rourke PP, Rodriguez LL, Schully SD, Shuldiner AR, Sze RK, Thakuria JV, Wolf SM, Burke GL.

Circ Cardiovasc Genet. 2010 Dec 1;3(6):574-80.

PMID: 21156933

Do return actionable results, no burden to look; similar to Bookman et al.

Chip SNPs of likely clinical relevance*

No requirement to look for these!

	GENE		rs	Chr	Illumin650	Illumin1Mil	MAF CEU	CHB	JPT	YRI
Factor V Leiden Thrombophilia	*F5*	R506Q	rs6025	1		x	0.01	0.00	0.00	0.00
MTHFR Thermolabile Deficiency	*MTHFR*	A222V	rs1801133	1	x	x	0.24	0.51	0.36	0.11
		E429A	rs1801131	1		x	0.36	0.20	0.18	0.10
Galactosemia	*GALT*	N314D	rs2070074	9	x	x	0.13	0.03	0.00	0.00
Hereditary Pancreatitis	*SPINK1*	N34S	rs17107315	5		x	0.00	0.00	0.01	0.00
G6PD Deficiency	*G6PD*	V68M	rs1050828	X		x	0.00	0.00	0.00	0.11
Hemochromatosis	*HFE*	H63D	rs1799945	6		x	0.18	0.13	0.04	0.00
			rs198846	*6*	x	x	0.14	0.04	0.06	0.18
			rs129128	*6*	x	x	0.14	0.04	0.02	0.00
		C282Y	rs1800562	6	x	x	0.04	0.00	0.00	0.00

***Johnson et al, Genet Med. 2010 Jun;12(6):355-63**

C&CC Return of Results Workgroup Recommendations

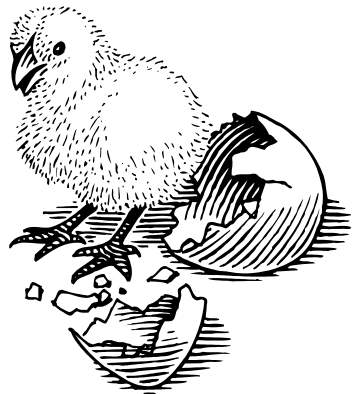
- Return of aggregate study findings to study participants encouraged
- Recommended establishment of Oversight Committee to deliberate on “clinically actionable” incidental and/or individual research results
  - “Actionable” = result with potential to change medical care
  - Excluding variation of reproductive significance to date (e.g., carrier status)
  - OC recommendations advisory, not binding, and subject to local IRB oversight and approval

Charge to Oversight Committee (10/09)

- Criteria for defining a “clinically actionable” result of direct benefit
- Considerations surrounding the return of non-CLIA certified research findings
- Appropriate methods for return, including when, to whom, and with what support for follow-up (including ways to avoid delivering unanticipated or unwanted information)
- Consultation & documentation

Initial deliberations-GWAS specific

- Preliminary Sex Chromosomal Anomalies identified by QC
  - Turner (XO, XO/XX, XXq-)
  - Klinefelter (XXY, XXY/XY) most common
- Two Mendelian genetic conditions potentially identifiable from current platforms
  - Hemochromatosis
  - Factor V Leiden (1M chip only)



Potentially actionable SCA results
Klinefelter Syndrome

- Associated with: Breast cancer, poor wound healing, diabetes, loss of bone density, thyroid diseases, testosterone imbalance, cardiac conditions, infertility
- Rx – testosterone, screening
- 4 of 10 known in EMR, one XXY/XY
- Of 6 potentially returnable
  - 1 deceased, 1 GU & testosterone RX in EMR
  - 4, PI decision at Mayo AGAINST return (to date)

Potentially actionable SCA results
Turner Syndrome

- Associated with: Hypertension, renal disease, cardiovascular malformations hearing and visual impairment, diabetes, thyroid diseases, infertility
- Rx - estrogen, screening, surgery as needed
- 2 clearer TS (XO, XXq-) known in EMR
- 8 other instances of mosaic XO/XX – acquired? – older (3 deceased), some with EMR findings not consistent (5 with kids); 1 infertile

1 M chip: Factor V Leiden, $F5_{G1691A}$

- Increased risk of venous clotting:
  homozygotes (40-80X)> heterozygotes (3-5X)
  - DVT, PE, 1st trimester pregnancy loss
- Interacts with other risk factors & thrombophilic mutations
- No consensus for population screening (this is not screening)
- Intervention:
  - Heterozygote: caution re: smoking/estrogens/pre-op/air travel
  - Homozygote: possible anti-coagulation
- Opinion: Homozygote potentially returnable (age?), heterozygote, not at this time

Hemochromatosis

- Autosomal recessive-penetrance 10% M, 1% F
  - Excess iron absorption; risk of iron overload →risk of cirrhosis, heart failure, diabetes, arthritis
- Not recommended for population screening; if screening pursued, Fe studies preferable to genotype
- Intervention: follow Fe levels, phlebotomy
- Opinion: Mixed, but generally return in males (age?)

eMERGE1 Results

	eMERGE Site				
Research Finding	Group Health Cooperative	Marshfield Clinic	Mayo Clinic	North-Western	Vanderbilt
Turner Syndrome XX-	4 mosaic 0 dx in EMR 3 deceased	2 mosaic 0 dx in EMR 1 infertile	0	0	4 (2 mosaic) 2 (XO, XXq-) dx in EMR
Klinefelter Syndrome 47, XXY	1 0 dx in EMR **deceased**	2 (1 XXY/XY) 1 dx in EMR	5 1 dx in EMR	1 dx in EMR	1 dx in EMR
Factor V Leiden rs6025 homozygotes	Not genotyped	Not genotyped	Not genotyped	Not reviewed	Not reviewed
HFE mutations rs1800562 homozygotes	Not reviewed due to older age (median 74 yrs)	14 (6 male) 5 (3) dx in EMR Rest: no Sx in EMR; no return	14 (7 male) 5 (3) dx in EMR No decision on return	6 (5 male) 2 (1) dx in EMR Not return, lack consent and contact	12 (6 male) 0 dx in EMR Unable to identify

Conclusions

- Paper: Fullerton et al, “minor revisions” submitted *Genetics in Medicine*
- Incidental findings remain a difficult issue; new genomic technologies will produce far more than GWAS
- “Clinically actionable” is debatable and may depend on individual context
- All politics are local
- eMERGE2 committees:
  - CERC and Actionable Variant
- Next: risk scores, pharmacogenetics

QC sex chromosome anomalies

SNP chr.	Va	Mar	May	GH	NW
~N	3061	3968	3,442	2829	3564
X0, X/Xq-	2	0	0	0	0
XX/XO	2	2-3	0	4	0
XXX	2	0	0	1	1
XXY ±LOH	2	0-1	5	1	0
XXY/XY	0	1	0	0	0
XYY	0	0	0	1	0

*Excludes LOH and gender mismatches, XXX and XYY not clinically actionable, dropped hereafter

XXY EMR follow-up: 4/9 “known”

Mayo	PAD	M	XXY	Very limited Mayo hx. No hgt/wgt or hx of family or sexual development, + venous/arterial vascular disease
Mayo	PAD	M	XXY	Hx compatible for XXY. No diagnosis. Single. No kids. No genital exam. + Aortofem bypass graft for atherosclerosis, bilat pedal edema, obesity, DMII.
Mayo	PAD	M	XXY	Mayo hx extremely limited. Married. No kids mentioned. No genital exam.
Vand	AD	M	XXY	Klinefelter syndrome
Vand	T2D 1M	M	XXY	absent left testicle and “suspicious” right testicle mass; testosterone therapy; no chr analysis d/t older age
GH	AD	M	XXY LOH X	Deceased. No Epic chart available. In other EMR no indication of karyotype tests, Klinefelter syndrome, infertility, or gynecomastia. No info re children.
Marsh	CAT	M	XXY/XY	Chart states Turner’s, but it is stated Klinefelter in the beginning of the chart.
Mayo	PAD	M	XXY; LOH X	Hx compatible for XXY. No diagnosis. No evidence he is aware of it. * Arterial bypass
Mayo	PAD	M	XXY; LOH X	Known XXY diagnosis

Turner EMR follow-up: 2/2 clear cases known

Site	Proj.	Psex	SNPs	EMR Review
Vand	T2D 660	F	Haploid Xq-	Karyotype shows 46XX, 23q-; Turner, premature ovarian failure; fertility issues
Vand	QRS	F	XO	Turner syndrome
GH	AD	F	XX/X0	Deceased. No Epic chart. In other EMR no indication of karyotype tests, Turner, reproductive or learning difficulties. No info re children.
GH	AD	F	XX/XO	Deceased. Two pregnancies, no children.
GH	AD	F	XX/XO	Still living. 4 children.
GH	AD	F	XX/XO	Deceased. No indication of karyotype tests, Turner's, reproductive problems or learning problems Very limited chart; No info re children.
Marsh	CAT	F	XX/XO	an attenuated androgen for sometime, difficulty getting pregnant, had 3 children
Vand	AD	F	XX/XO	Mention of children
Marsh	CAT	F	XX/XO	EMR at age > 50. c/o ovaries (?producing too much estrogen). Unable to conceive.
Vand	QRS	F	XX/XO	Mention of a son; hysterectomy and oophorectomy

Potentially returnable* Klinefelter

Site	Proj	Psex	Notes	EMR Review
Mayo	PAD	M	XXY	Hx limited. No hgt/wgt or hx of family or sexual development
Mayo	PAD	M	XXY	No diagnosis. Single. No kids. No genital exam.
Mayo	PAD	M	XXY	Hx limited. Married. No kids mentioned. No genital exam.
Mayo	PAD	M	XXY; LOH	No diagnosis.
GH	AD	M	XXY; LOH	Deceased.

*Subjects may know, just not in EMR

Mayo follow-up: did not utilize ROROC initially

- Laney and Barbara provided the Mayo perspective on Klinefelter to the ROROC.
- Input from a Mayo endocrinologist and a Mayo psychiatrist on the issue of result return for this condition.
- The endocrinologist recommended return of results, due largely to the established efficacy and benefit of therapies.
- The psychiatrist's viewpoint was very different; due to the "delicate nature" of Klinefelter, the psychiatrist suggested great care be taken when considering return. In the statement, it was suggested that the condition affects psychosocial interactions and gender identity so pervasively, that the benefit of result return may not be greater than the damage done following diagnosis. Some concern over possible nonpaternity.
- We advised discussion with Mayo persons who return incidental results. XXY patients may be consulted.
- Mayo biobank is evaluating this issue. IRB will be engaged in this decision.

Factor V Leiden, $F5_{G1691A}$

Increased risk of venous clotting (hets 5x, about 1% of hets), particularly for homozygotes (40-80X, pregnancy related VTE 9%).

DVT, PE, 1st trimester pregnancy loss

Interacts with smoking, hormone status surgery, and other thrombophilic mutations

Not included in screening

Intervention: more tests, ?aspirin, movement, cautions for smoking and estrogens, ?pre-op

Opinion: Homozygote potentially returnable (age?), heterozygote, not at this time

Hemochromatosis

Autosomal recessive-low penetrance
(C282Y/C282Y, 2%; other genotypes less)

liver, heart, diabetes, arthritis

Fe absorption; less penetrant in females.

Not included in screening

Can be screened for: Fe studies(not specific)

Intervention: follow levels, phlebotomy

Opinion: Still under consideration (low penetrance but actionable); to discuss with those who rejected screening

CLIA

- Significant conflict on legal need for CLIA to return research results not originally intended to return (unresolved)
  - Standard of practice
- Agreement that if you intend ROR for clinical use (e.g put in EMR) from the start that CLIA lab is needed (sample issues)