Considerations for the Return of Genomic Results

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PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

BWH

HARVARD MEDICAL SCHOOL

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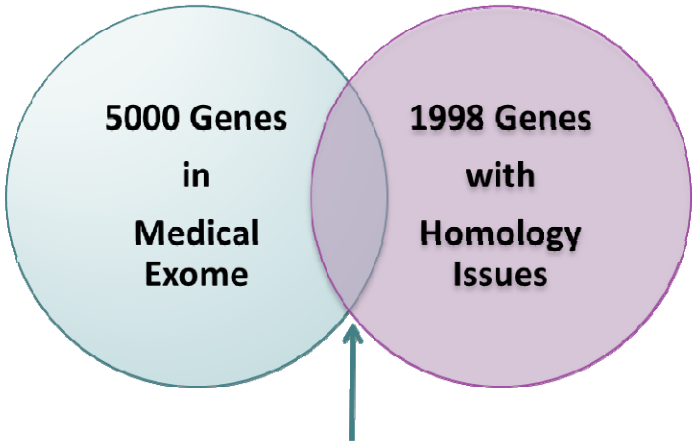
Challenges to scaling genomic interpretation and ROR

Technical validity and sample identity

- Orthogonal confirmation with original sample addresses issues that happen even with CLIA NGS
  - Analytical validity of results
    - SNVs challenging in homologous regions
    - InDels often challenging
  - Sample mix-ups during testing process



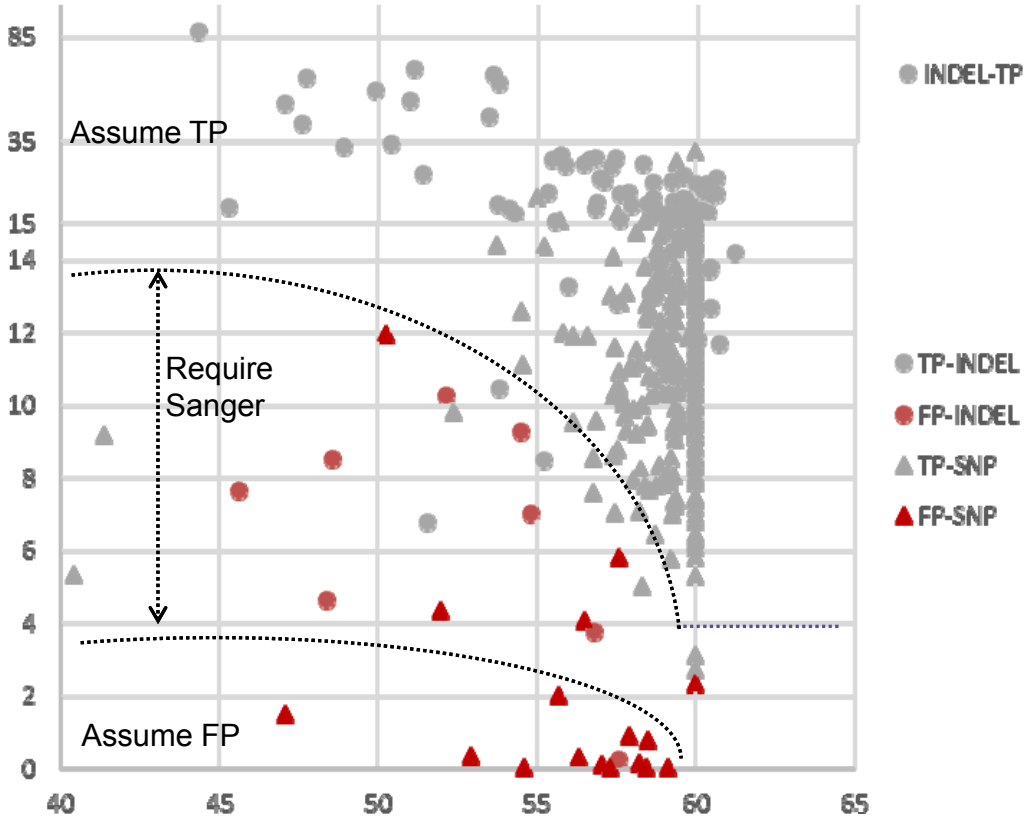
(e.g. PMS2, SMN1/2, VWF, STRC)

Courtesy: Diana Mandelker and Birgit Funke

- Yet, duplicate specimens and orthogonal confirmation are not scalable

→ Consider making some data available separately as unconfirmed research results requiring CLIA confirmation

Quality Scores for NGS Data – When is Sanger required?



Whole Genome Variants

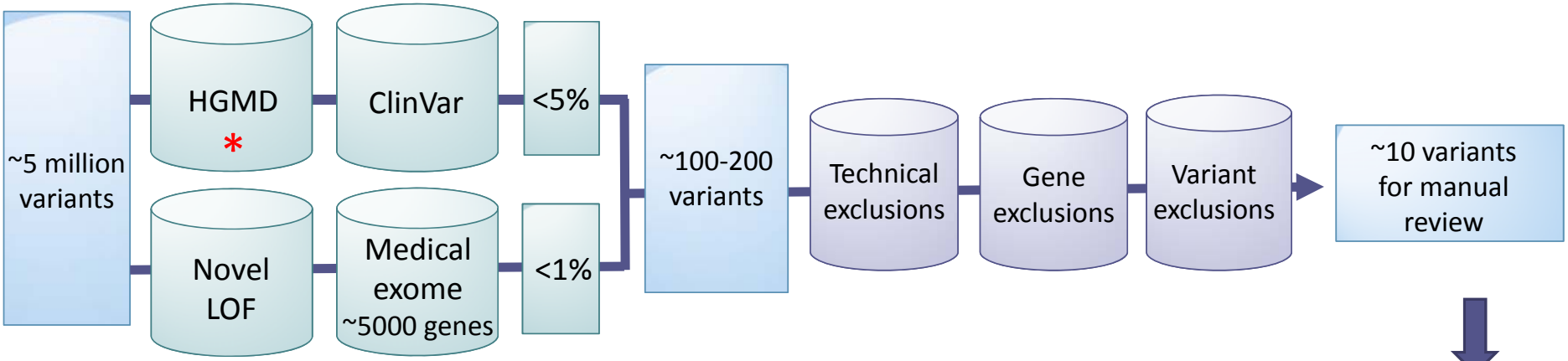
373 Assume True Positive

31 Require Sanger (7.4%)

13 Assume False Positive

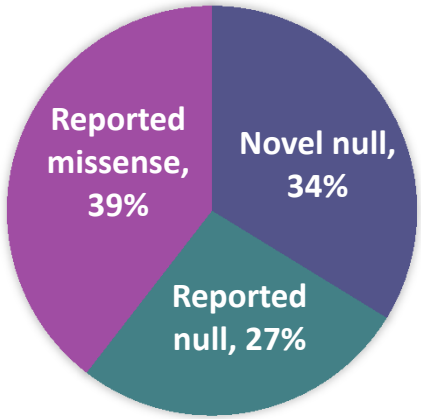
417 Total

MedSeq Variant Analysis Pipeline and Detection Rates



**In non-diagnostic testing, 92% of variants reported as pathogenic in HGMD had insufficient evidence to support the claim.*

Variant Type	Average Review Time
Variant with literature	90 min
Variant with no literature	26 min



Several hours of review per genome

~2% (0-7) of filtered variants reported in MedSeq

Pathogenic
Likely Pathogenic
VUS – Favor Pathogenic

Interpretation Differences in ClinVar

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

ClinGen — The Clinical Genome Resource

Heidi L. Rehm, Ph.D., Jonathan S. Berg, M.D., Ph.D., Lisa D. Brooks, Ph.D., Carlos D. Bustamante, Ph.D., James P. Evans, M.D., Ph.D., Melissa J. Landrum, Ph.D., David H. Ledbetter, Ph.D., Donna R. Maglott, Ph.D., Christa Lese Martin, Ph.D., Robert L. Nussbaum, M.D., Sharon E. Plon, M.D., Ph.D., Erin M. Ramos, Ph.D., Stephen T. Sherry, Ph.D., and Michael S. Watson, Ph.D., for ClinGen

NEJM May 27th, 2015

11% (12,895/118,169) of variants have ≥2 submitters in ClinVar

↓

17% (2229/12,895) are interpreted differently

26% (97,422/377,075) of variants have ≥2 submitters in ClinVar

↓

17% (16,631/97,422) are interpreted differently

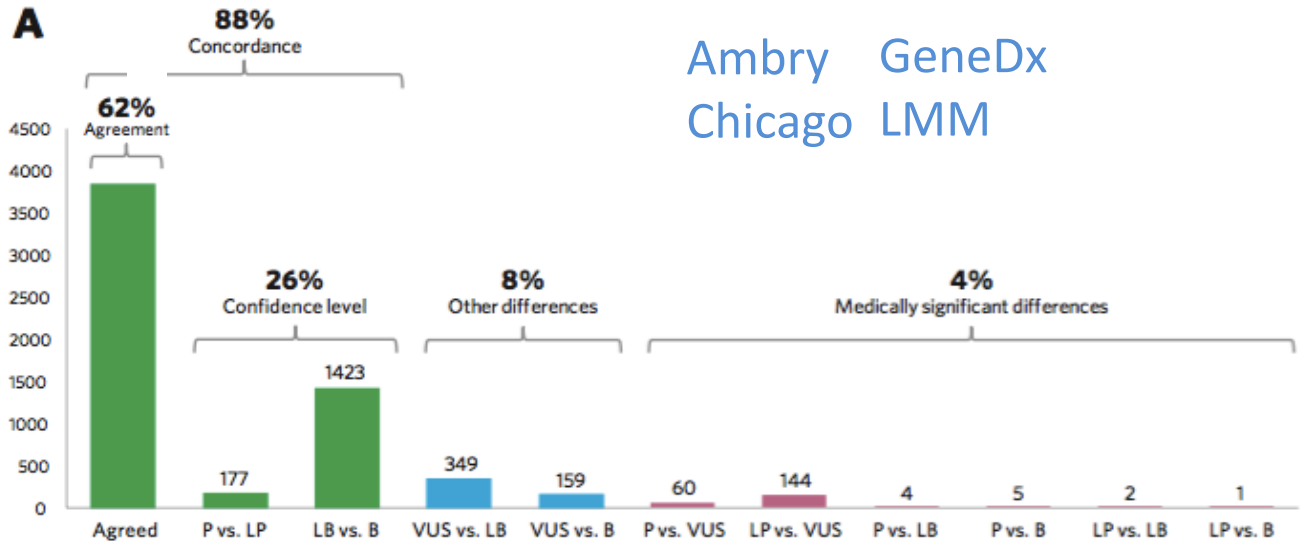
↓

3.6% medically significant (P/LP vs VUS/LB/B)

↓

1.7% medically significant among clinical lab submissions

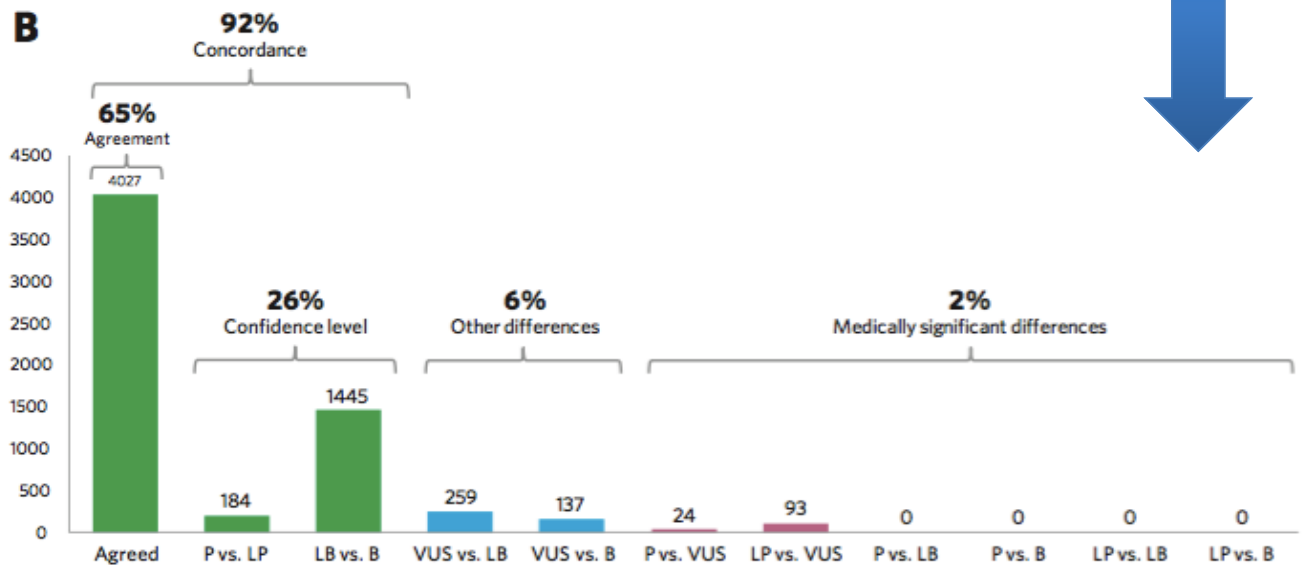
Pre-
Discrepancy
Resolution
Process



Ambry GeneDx
Chicago LMM

Steven
Harrison

Post-
Discrepancy
Resolution
Process



87% resolution (211/242)

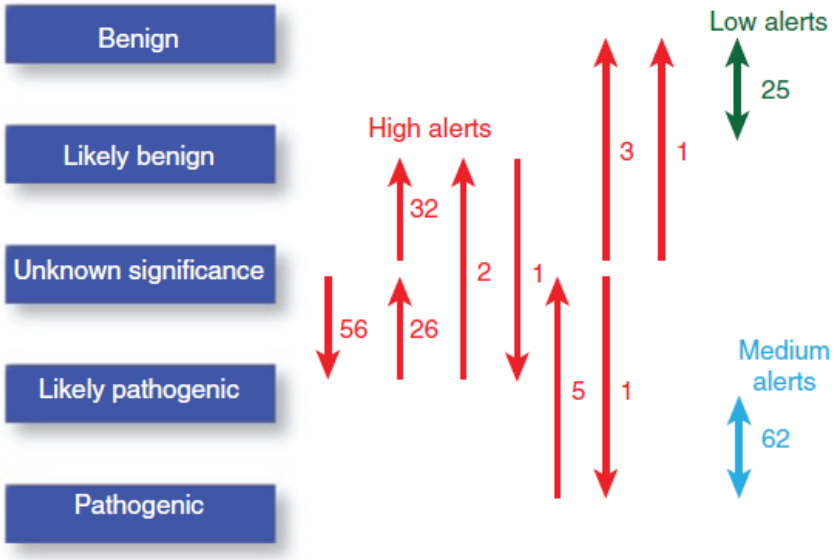
Harrison et al.
Genet Med, in press

Variant Knowledge Evolution

Communicating new knowledge on previously reported genetic variants

Samuel J. Aronson, ALM, MA[1,2], Eugene H. Clark, BM[1,2], Matthew Varugheese, MS[1,2], Samantha Baxter, MS, CGC[3], Lawrence J. Babb, BS[1,2] and Heidi L. Rehm, PhD, FACMG[3,4]

Variant classification changes—HCM data



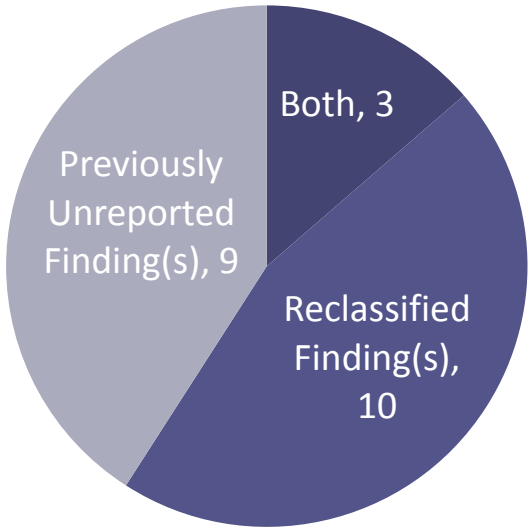
~4% of cases per year received medium or high alerts

Genet Med. Apr 2012 PMID: 22481129

Genetics inMedicine

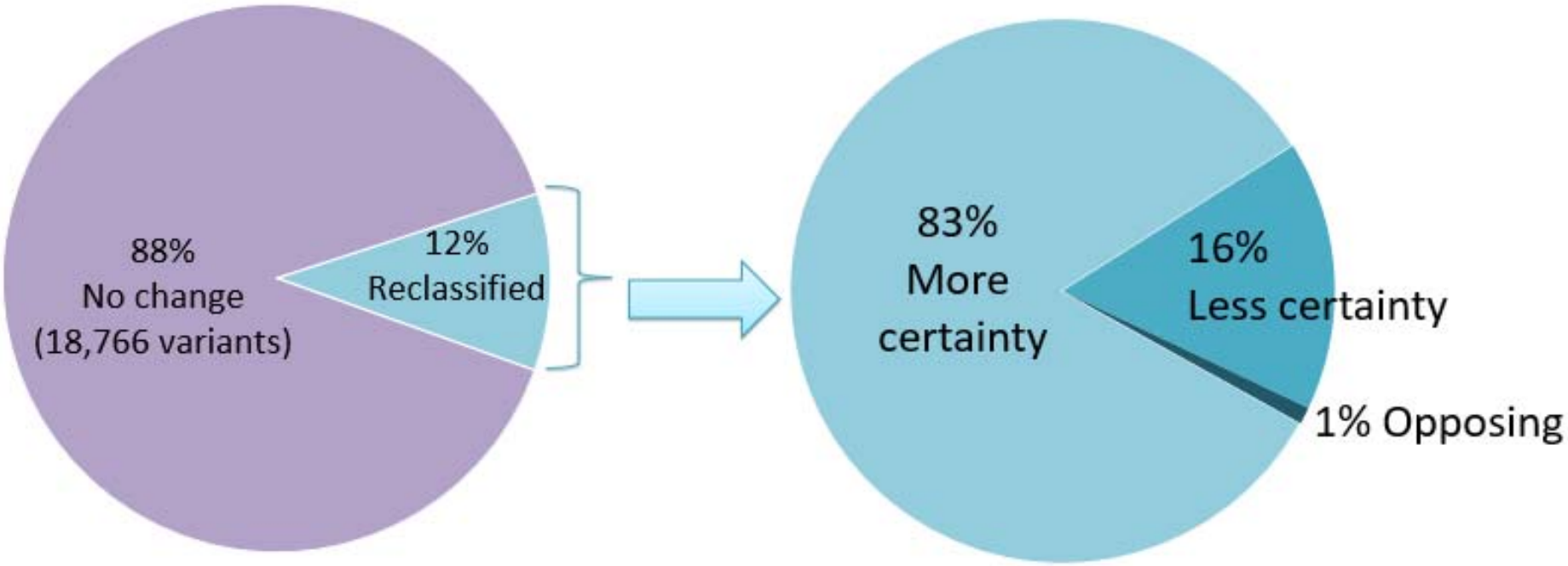
MedSeq Genome Reanalysis

22% (22/100) Participants Received New or Reclassified Variants



Expert Panel interpretations sometimes change as well

Variant Reclassification Over 12 Years at the Laboratory for Molecular Medicine



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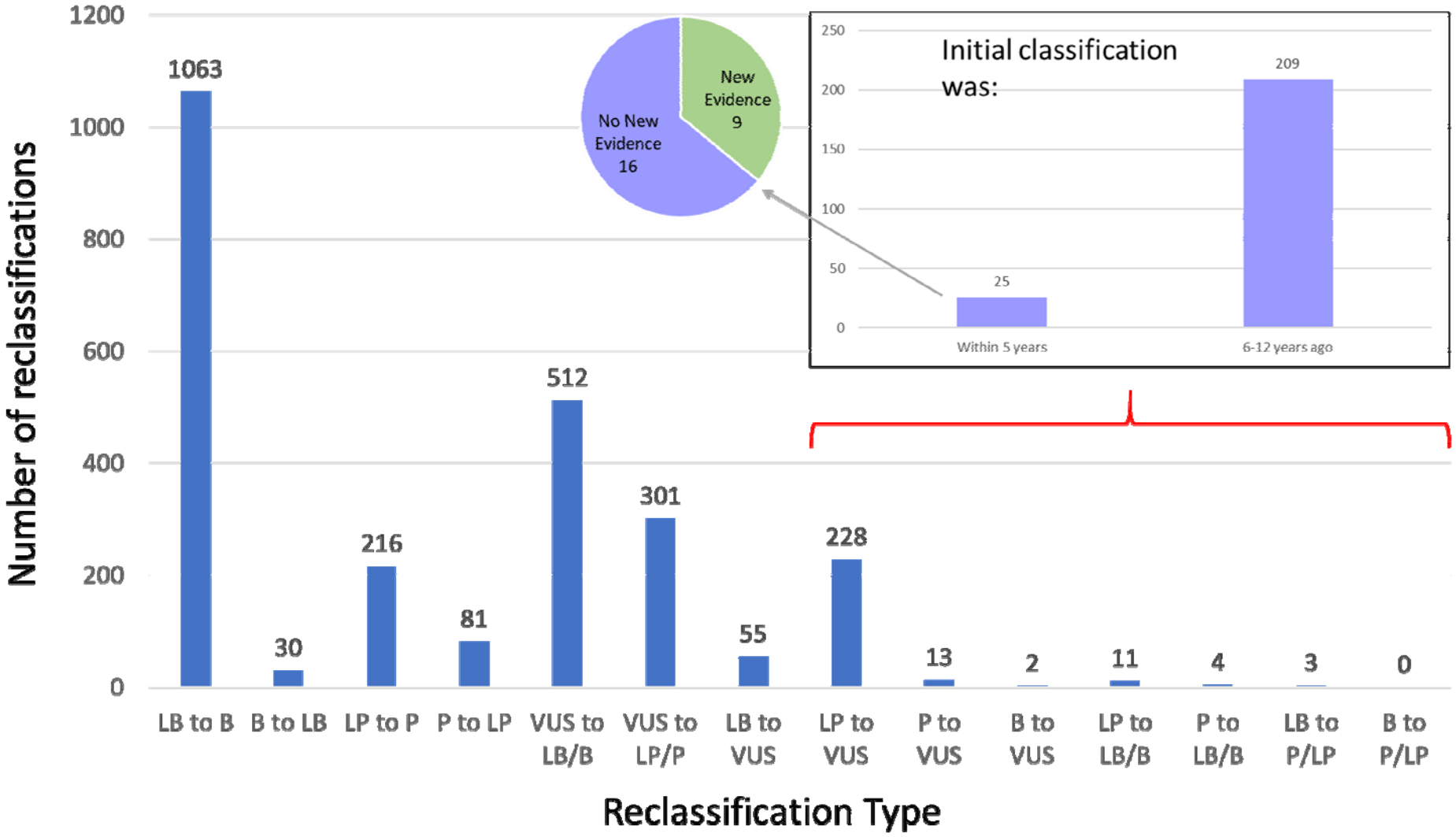
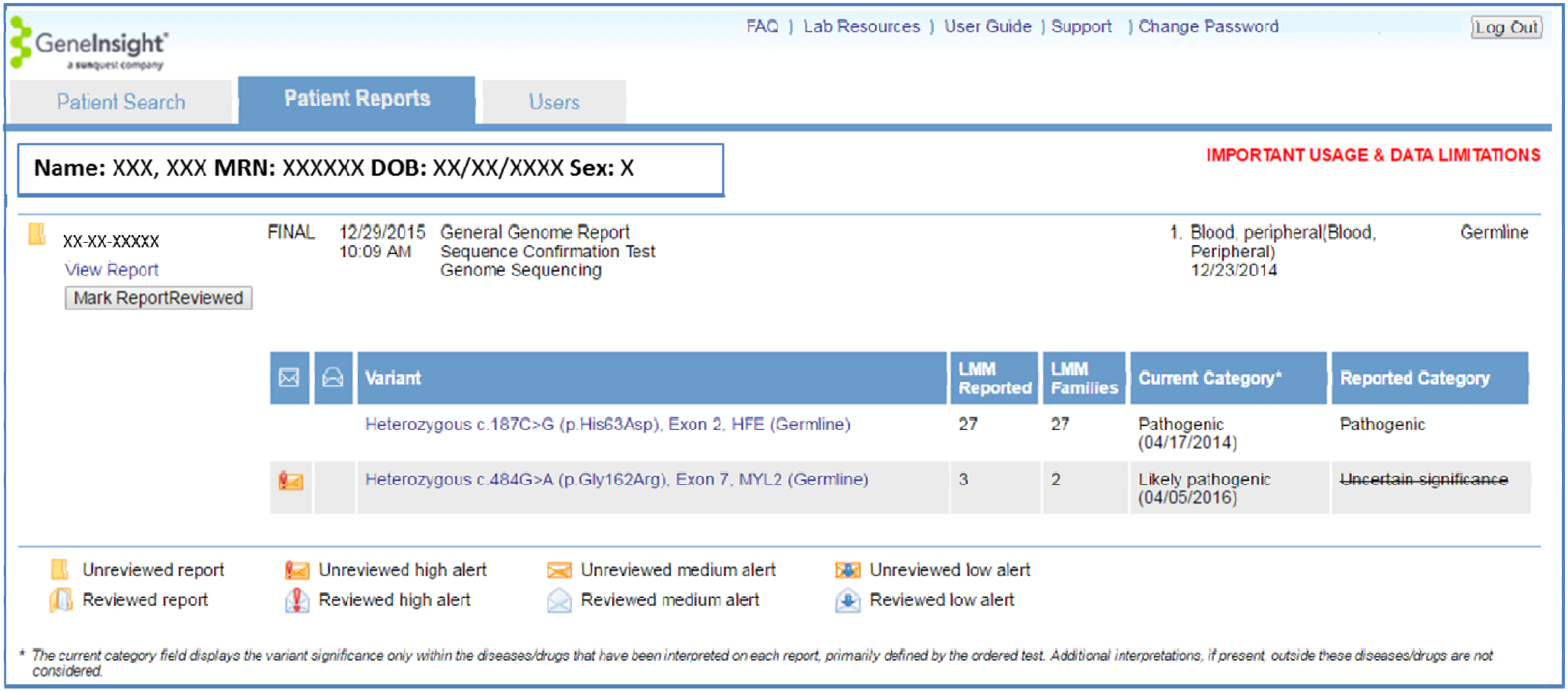


Laboratory management of knowledge updates

1. Issue amended reports
2. Allow direct access to laboratory database (e.g. Emory)
3. Regularly deposit variants into ClinVar
4. Deliver automated knowledge updates on reported variants (e.g. GeneInsight)

Reports, Structured Variant Data and Variant Updates Returned Via EHR (GeneInsight Clinic)



GeneInsight
a sunquest company

FAQ | Lab Resources | User Guide | Support | Change Password | Log Out

Patient Search | **Patient Reports** | Users

Name: XXX, XXX **MRN:** XXXXXX **DOB:** XX/XX/XXXX **Sex:** X

IMPORTANT USAGE & DATA LIMITATIONS

XX-XX-XXXXX
View Report
Mark ReportReviewed

FINAL 12/29/2015 10:09 AM General Genome Report
Sequence Confirmation Test
Genome Sequencing

1. Blood, peripheral(Blood, Peripheral) 12/23/2014 — Germline

		Variant	LMM Reported	LMM Families	Current Category*	Reported Category
		Heterozygous c.187C>G (p.His63Asp), Exon 2, HFE (Germline)	27	27	Pathogenic (04/17/2014)	Pathogenic
		Heterozygous c.484G>A (p.Gly162Arg), Exon 7, MYL2 (Germline)	3	2	Likely pathogenic (04/05/2016)	~~Uncertain significance~~

Unreviewed report | Unreviewed high alert | Unreviewed medium alert | Unreviewed low alert
Reviewed report | Reviewed high alert | Reviewed medium alert | Reviewed low alert

* *The current category field displays the variant significance only within the diseases/drugs that have been interpreted on each report, primarily defined by the ordered test. Additional interpretations, if present, outside these diseases/drugs are not considered.*

Updated Variant Information

Reported Variant Interpretation History (Variant 2 of 2) IMPORTANT USAGE & DATA LIMITATIONS

Warning: This page only lists information on a single variant. This is outside of the patient report context and may be insufficient for re-interpretation of the patient report.

Heterozygous c.484G>A (p.Gly162Arg), Exon 7, MYL2 (Germline)

Patient
Report
Laboratory Laboratory for Molecular Medicine
Counts Reports (3), Families (2)

Current Category*	Reported Category
Likely pathogenic	~~Uncertain significance~~

Alerts

Status	!	Alerted	Message
Unreviewed	!	04/05/2016 02:13 PM	The category for the MYL2 c.484G>A (p.Gly162Arg) association to Hypertrophic cardiomyopathy changed from Uncertain significance to Likely pathogenic. Reason for Update: New Evidence. Approved by: Birgit Funke.

Mark AlertsReviewed

Current Knowledge** Approved 04/05/2016 02:13 PM by Birgit Funke

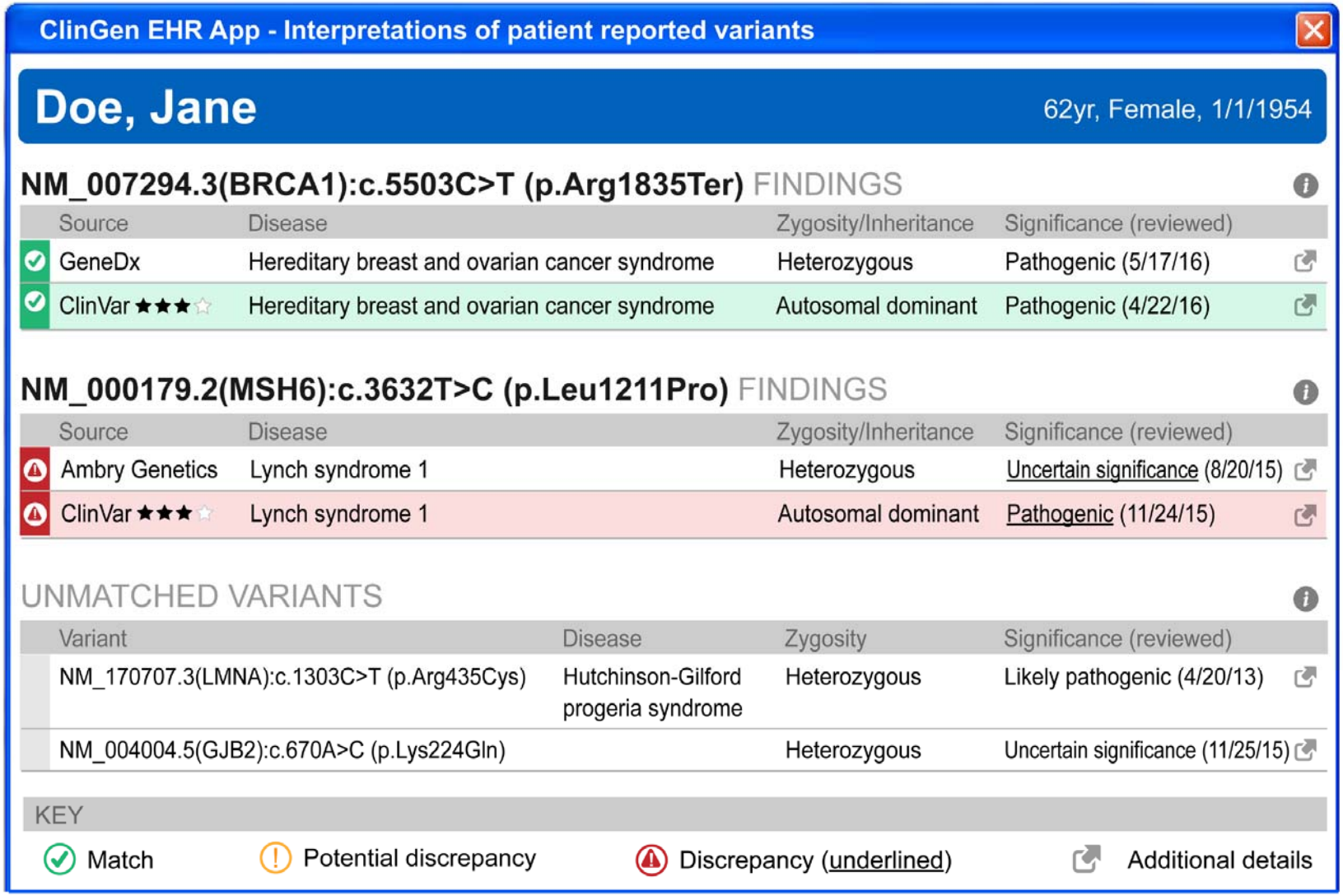
Category	Diseases/Drugs	Variant Interpretation
Likely pathogenic	Hypertrophic cardiomyopathy	The p.Gly162Arg variant in MYL2 has been reported in 1 individual with HCM (Olivotto 2008). It has also been identified by our laboratory in 1 individual with LVH, reduced EF and ST segment abnormality and occurred de novo in another individual with HCM, AV block and RBBB (LMM unpublished data). This variant was absent from large population studies. In vitro functional studies provide some evidence that the p.Gly162Arg variant may impact protein function (Burghardt 2013). However, these types of assays sometimes do not accurately represent biological function. Glycine (Gly) at position 162 is highly conserved in evolution and the change to arginine (Arg) was predicted to be pathogenic using a computational tool clinically validated by our laboratory. This tool's pathogenic prediction is estimated to be correct 94% of the time (Jordan 2011). In summary, although additional studies are required to fully establish its clinical significance, this variant is likely pathogenic.

* *The current category field displays the variant significance only within the diseases/drugs that have been interpreted on each report, primarily defined by the ordered test. Additional interpretations, if present, outside these diseases/drugs are not considered.*

** *The Current Knowledge only includes the following Diseases/Drugs Interpreted on Report: General Genome Report Disease, Hypertrophic cardiomyopathy, Hereditary hemochromatosis*

Prototype of a proposed EHR App

Will bring in 3-4 star variants from ClinVar



ClinGen
Clinical Genome Resource

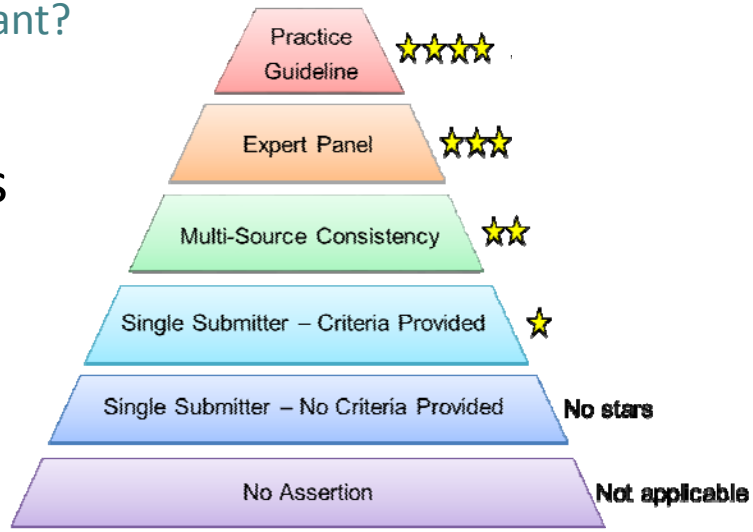
Proposal for AoU Genetic ROR

- Begin with a small set of results that reach consensus for utility and sufficient evidence
- Label “clinical” and expand scope once a successful process is achieved
  - ACMG59 as starting point
  - Pathogenic as starting point

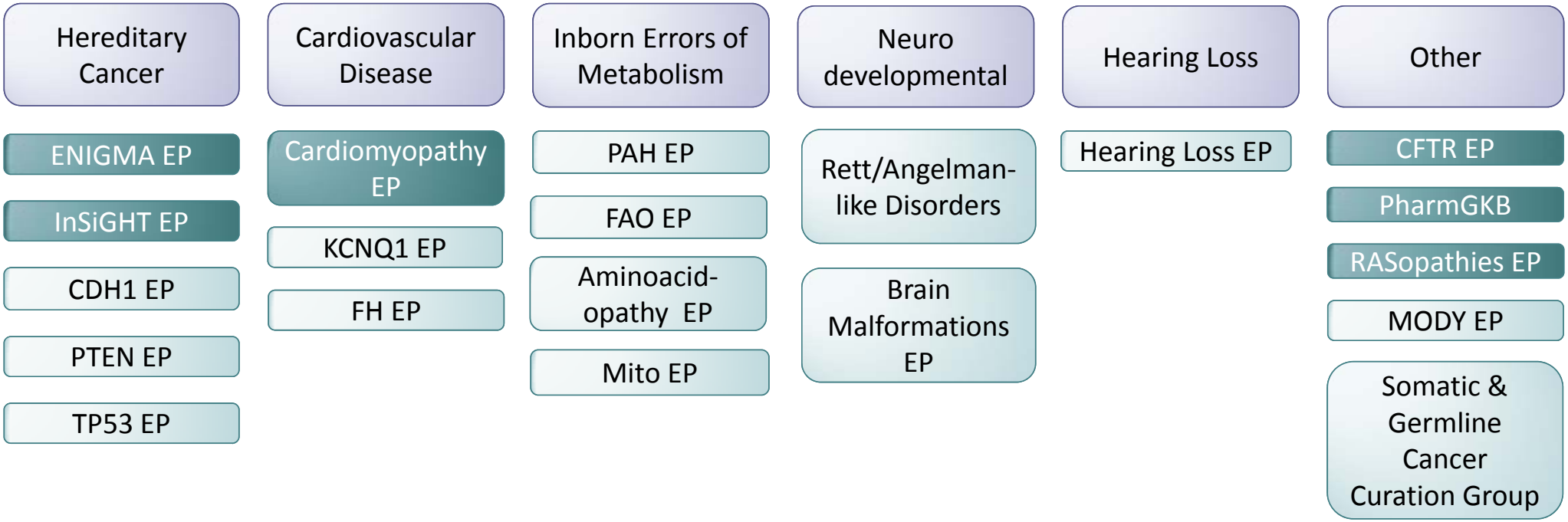
- Consider approaches to share additional data – label as “research”
  - Enable participants to share their raw data broadly
    - Array genotypes, BAMs, VCFs
    - List of annotated novel, rare or suspicious variants
  - Allow access to data when clinical context raises the prior probability of disease
    - CLIA confirmations and interpretations can be ordered as needed
  - Enable other studies that can delve deeper into the significance of these variants

Approaches to scale genomic interpretation

- For novel predicted null variants, checklist can largely be automated if gene and exon level curation is performed in advance
  - ✓ Are null variants an established mechanism of disease?
  - ✓ How frequently are predicted null variants found in the gene in large population databases? Het vs hom? What is the constraint score in ExAC?
  - ✓ Are there other known pathogenic variants in the exon? Also check ExAC for nulls in that exon.
  - ✓ Is nonsense-mediated decay predicted?
  - ✓ Are there predicted null variants reported 3' (and 5') to the variant?
  - ✓ Is the exon alternatively spliced?
- Rely on ClinVar review levels for reported variants
  - Consider reporting only 3 star or 4 star variants
  - Could add 2 star variants (all submitters agree)



Variant Curation Expert Panels (ClinGen-approved and in planning)



Application approved by ClinGen for 3 star ★★★ submissions to ClinVar

Planning to apply to ClinGen for 3 star submission level

9318 expert reviewed variants in ClinVar (2.5%)

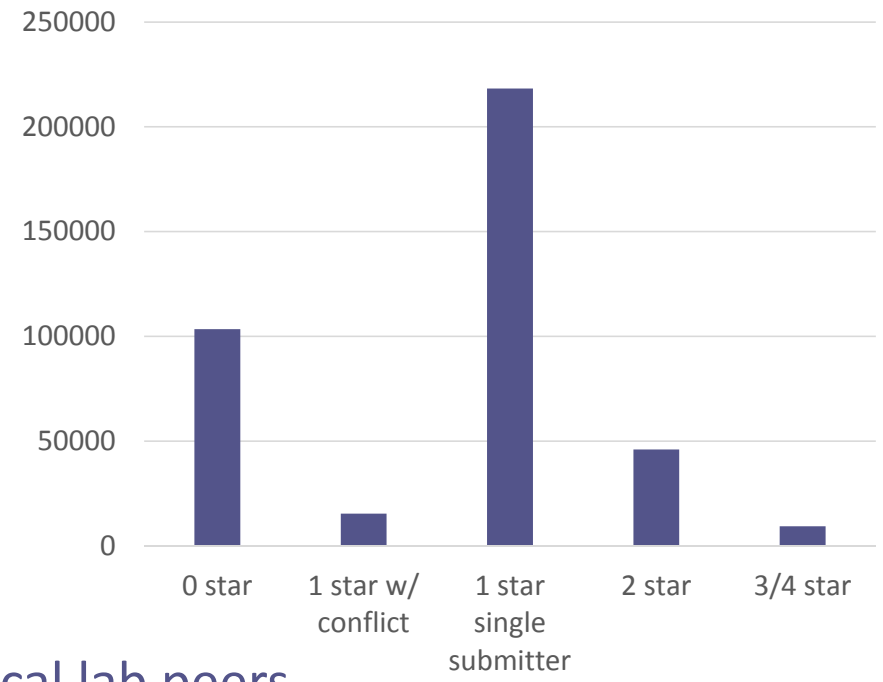
Which 1-2 star variants to report?

- Not all 2 star variants are created equal
- Not all 1 star variants are created equal

- 2 star: How many labs agree? Only 2 or many?

- Which groups(s) reported?
  - Single submitter criteria provided (1 star)
  - Experienced clinical lab
    - subjective – opinion of physicians and clinical lab peers
    - objective measures – volume of submissions in a disease area (data from ClinVar Miner)

- Date of last evaluation (evaluated within last 1-2 years)



hu025CEA (Heidi Rehm) - GET-Evidence variant report– PGP Project

http://evidence.pgp-hms.org/genomes

Genome report

Variant	Clinical Importance	Impact	Allele freq	Summary
APOE-C130R	High	Well-established pathogenic Complex/Other, Heterozygous	14%	This is generally known as the ApoE4 allele of ApoE and is associated with increased risk of Alzheimer's. 20-25% of individuals are heterozygous for this variant, and 1-2% are homozygous. Data from Khachaturian et al. suggests a [illegible] 40% of ApoE4 homozygotes (Alzheimer's by the age of 100 earlier for heterozygous carri
NOD2-R702W	Low	Likely pathogenic Complex/Other, Heterozygous	3.30%	NOD2 encodes a protein invo
MBL2-R52C	Low	Likely pathogenic Recessive, Carrier (Heterozygous)	4.90%	This variant is associated with compound heterozygous are this gene is known as variant
APOA5-S19W	Low	Likely pathogenic Unknown, Heterozygous	6.50%	This variant, also known as A
MTRR-I49M	Low	Likely pathogenic Recessive, Carrier (Heterozygous)	45%	This common variant (HapM position). Mothers homozyg plays a far larger role in the r associating this variant with i
CD40LG-G219R	Low	Uncertain pathogenic Recessive, Carrier (Heterozygous)	1.10%	Study of a single family with any. Because 2% of males ca

Insufficiently evaluated variants (3319 variants)

Variant	Prioritization score	Allele freq	Num of articles	Zygosity and Prioritization Sc
MC2R-S74I	5	0.02%		Heterozygous. In OMIM, Poly
NEFL-S472Shift	4			meshift, Tes
RSPH4A-W607Shift	4			meshift, Te
TTN-E190Shift	4			meshift, Te
XDH-R1296W	4			s unevaluat
CEP290-E277Q	4	1.40%		Heterozygous. Polyphen 2: 0.
DPYD-S534N	4	1.60%	2	Carrier (Heterozygous). Has u
CEP290-K838E	4	3.20%		Heterozygous. Has unevaluat
LAMC2-D247E	4	3.40%	1	Heterozygous. Has unevaluat
F5-P140				
COL11A				
IL23R-R				
ATP8B1				
RDH12-R161Q	4	12%		Heterozygous. Has unevaluat
SPG7-R688Q	4	14%	3	Carrier (Heterozygous). In Ph
SPG7-T503A	4	14%	1	Heterozygous. In PharmGKB,
DLL3-F172C	4	15%		Heterozygous. Has unevaluat
MSH6-G39E	4	18%	3	Heterozygous. Has unevaluat
ATP7A-V767L	4	25%	1	Heterozygous. In PharmGKB,
GPR98-Y2232C	4	32%		Heterozygous. Has unevaluat
NHLRC1-P111L	4	34%		Heterozygous. Has unevaluat

Technical artifact

Variant 56 of 3319: MYH7-R1500W 3 ? Heterozygous. Polyphen

Case	Source	Year	Dx	Age Dx	Segregation	Clinical hx; Family
1	Karkkainen	2004	DCM	55 yr	not tested	mother heart failure/car several family members
2	Jerosch-Herold	2008	DCM	56 yr	2	mother symptoms at 95 consistent with DCM) an 73 of HF) and 63 yr (dysp
3	Merlo	2013	DCM	?	?	
4	Hazebroek	2015	DCM	? (>18 yr)	?	
5	LMM	2013	DCM/LVNC	32 yr	no fam hx	past hx of IV drug use; ej improved
6	GeneDx	20??	DCM	<13 yr	homozygous	
7	GeneDx	20??	DCM			
8	GeneDx	20??	DCM			
9	Invitae	2015	DCM/LVNC	34 yr Hispanic	no fam hx	peripartum cardiomyopa hypothyroidism; heart ha thyroid treatment but sti list
10	Geisinger	2016				

Supporting Participants with a Genomic Result & Their Clinicians – Principles & Implications for *All of Us*

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@andyfaucett

Relevant *All of Us* guiding principles

- "focus not just on disease, but also on ways to increase an individual's chances of remaining healthy throughout life"
- "empower study participants with data and information to improve their own health"

Geisinger MyCode Participant Driven Principles

- Participant focus groups:
  - Wanted Geisinger to guide project
  - Comfortable receiving ALL results
  - Accepted we do not understand some results
  - Importance of placing genomic results in EHR
  - Share results with participants
  - Education, medical support to patients & clinicians

Faucett WA & Davis FD, 2016, *Appl Trans Genom*

Engagement to Develop Return Process

- Patient focus groups
- Ethics Advisory Council (EAC)
- Clinical Oversight Committee (COC)
- Precision Health Patient Advisory Board

Faucett WA & Davis FD, 2016,
Appl Trans Genom

Applied & Translational Genomics

Volume 8, March 2016, Pages 33–35

Open Access

How Geisinger made the case for an institutional duty to return genomic results to biobank participants

W. Andrew Faucett, F. Daniel Davis

Show more

http://dx.doi.org/10.1016/j.atg.2016.01.003

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To return or not to return the results of genomics research: that has been the question at the crux of an ongoing debate spawned by the increasingly rapid evolution of genomics. [1] Like many debates, this one arises from conflicting perspectives on broader concerns: for example, the purported distinction between research and patient care, the relationship between health care institutions and the communities they serve, and the role of patient- and research-participant-engagement in such debates (and in their resolution).

Principles of MyCode Genomic Results Program

1. Geisinger expert consensus on which genes to evaluate & return
2. Pathogenic/likely pathogenic variants in medically actionable genes
3. Minimize false positives (specificity > sensitivity)
4. Patients choose how to follow up clinically
5. Supportive infrastructure for patients & clinicians

Result return process

1. Primary care clinician notified of result via EHR
2. Patients notified in writing that result is available
3. Clinical Genomics team calls patients
    1. Disclose nature of results
    2. Schedule follow-up (detailed disclosure, clinical eval)
    3. Encourage family communication of results
4. Patients choose clinical follow-up approach
5. All patients receive educational/supportive materials on relevant genetic condition
6. Care coordination with co-managing clinicians

Patient Support

- Multiple service delivery models
- Genetic counselors available for phone consults 5 days/ week
- Genetic counselors & physician geneticists available for in-person consults 3 days/week
- Genetic Counselor for most results
- Triage conditions with syndromic features to geneticists

Lessons – MyCode Patient Support

Follow-up Status	Positive Results	%
Clinical Genomics	245	45%
PCP or specialist	73	13%
Declined immediate follow-up	134	25%
Lost to follow-up	38	7%
Deceased/Withdrawn	9	2%
In Process	45	8%
Total	544	100%

Results Returned

MyCode® results returned

544 patient-participants have received results* from the Genomic Screening and Counseling Program

Geisinger mycode | 150,000+ PARTICIPANTS

For the latest results, see go.geisinger.org/results.

Jan. 1, 2018

Risk condition	Patients per risk condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)	203	*BRCA1*	68
		BRCA2	135
Familial hypercholesterolemia (early heart attacks and strokes)	92	*APOB*	31
		LDLR	61
Lynch syndrome (early colon, uterine and other cancers)	50	*PMS2*	18
		MSH6	23
		MSH2	6
		MLH1	3
Cardiovascular risk			
Cardiomyopathy (diseases of the heart muscle with dangerous complications)	53	*MYH7*	8
		MYBPC3	29
		TPM1	2
		TNNI3	3
		TNNT2	5
		MYL3	4
		LMNA	2
Arrhythmia (irregular heartbeat with risk for cardiac arrest)	38	*SCN5A*	20
		KCNQ1	13
		KCNE1	2
		KCNH2	3
Arrhythmogenic right ventricular cardiomyopathy (disease of the heart muscle with risk for cardiac arrest)	27	*DSP*	12
		PKP2	13
		DSG2	1
		DSC2	1
Marfan syndrome (connective tissue disease that can cause heart, eye, and skeletal problems)	4	*FBN1*	4

(continued on next page)

MyCode® results returned *(continued)*

Jan. 1, 2018

544 patient-participants have received results* from the Genomic Screening and Counseling Program

Risk Condition	Patients per risk condition	Gene	Patients per gene
Cardiovascular risk *(continued from front)*			
Heritable thoracic aortic disease (genetic predisposition to weakening of the wall of the aorta, leading to swelling and sometimes rupture)	8	*ACTA2*	8
Cancer risk			
Hereditary pheochromocytomas and paragangliomas (tumors that can release extra hormones and, rarely, become cancer)	10	*SDHB*	4
		SDHC	3
		SDHD	3
Multiple endocrine neoplasia type 1 (tumors that can release extra hormones and, rarely, become cancer)	5	*MEN1*	5
Multiple endocrine neoplasia type 2 (early thyroid cancer)	17	*RET*	17
PTEN hamartoma tumor syndrome (early breast, thyroid, uterine and other cancers, with intellectual disability in some cases)	3	*PTEN*	3
Tuberous sclerosis (multiple types of benign [non-cancer] tumors)	1	*TSC2*	1
Li-Fraumeni syndrome (early breast, soft tissue, brain, adrenal and other cancers)	8	*TP53*	8
Familial adenomatous polyposis (early colon cancer)	2	*APC*	2
Von Hippel-Lindau (early kidney cancer and benign tumors of brain, eye, pancreas and adrenal gland)	1	*VHL*	1
Other			
Malignant hyperthermia (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)	22	*RYR1*	22
Fabry disease (enzyme defect leading to damage of blood vessels in the skin and cells in the kidneys, heart, and nervous system)	1	*GLA*	1
Vascular Ehlers-Danlos (disease of the connective tissues, including arteries and muscles, that can increase the risk for health complications, such as rupture of arteries)	1	*COL3A1*	1
Hereditary hemochromatosis (too much iron in blood, can lead to liver and heart problems)	1	*HFE*	1
Totals	547		547

Support in MyCode Genomic Results Program

- Patient support
  - Opportunity to meet with clinical genomics team
  - Family history intake
  - Condition-specific multi-disciplinary clinics
- Clinician support
  - EHR tools for detailed phenotyping, documentation
  - Continuing Medical Education
  - Opportunity to consult clinical genomics team
- Both
  - Provider / Patient friendly genomic reports

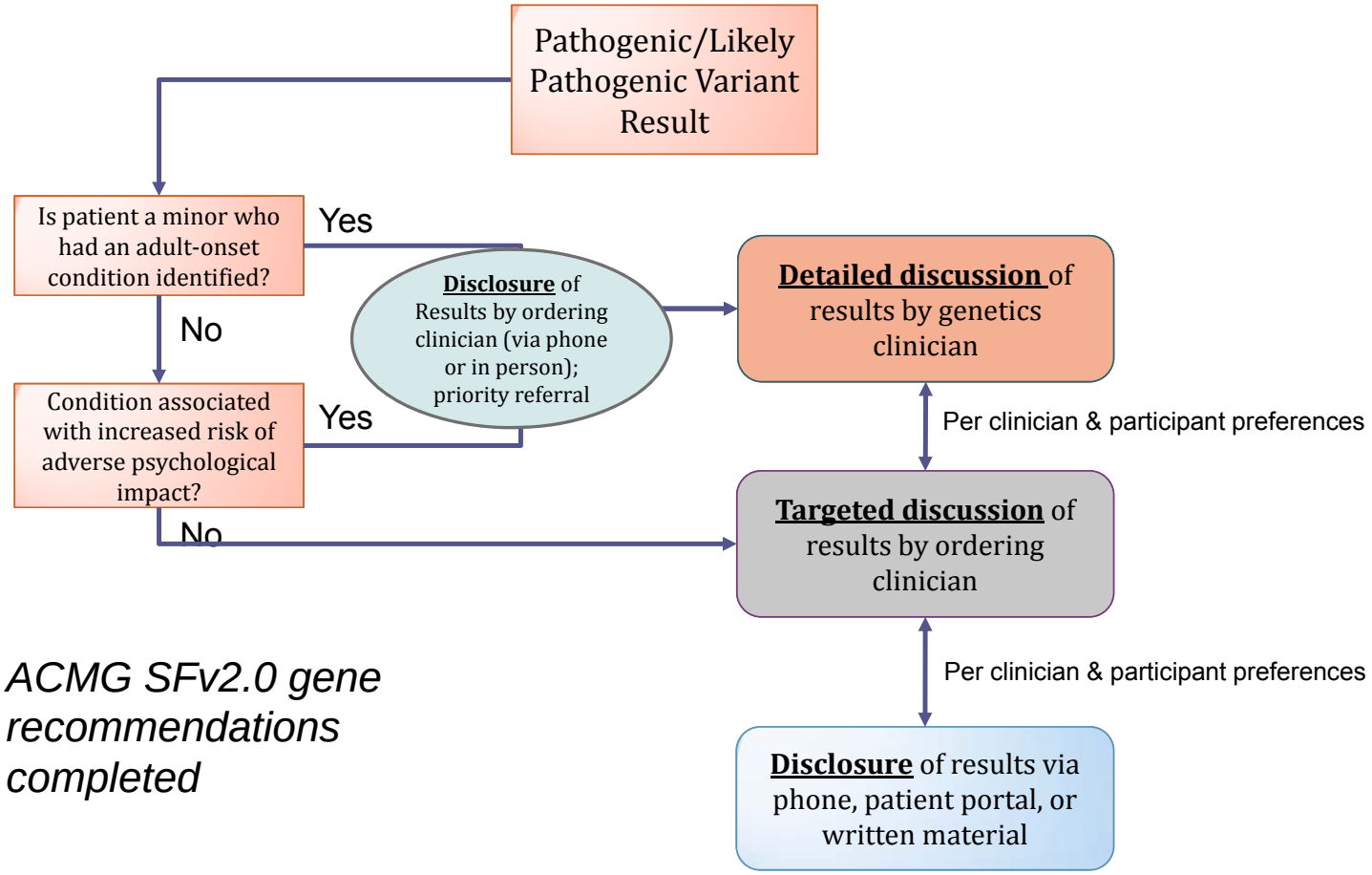
Lessons – MyCode Patient Support

- Positive feedback from qualitative interviews
  - "[I]t's a good thing to know for you and your family members…if you find something you can nip in the bud, it's not nearly as expensive"
  - "Nobody's been very upset or even my kids who have potential of having it themselves have been very laid back about it actually"
- Facilitating cascade testing is challenging

MyCode Clinician Support

- CME modules
  - Low uptake, but want to know they are there
  - PCPs prefer brief, risk management focused on support
- PCPs prefer Genomics disclose results & guide evaluation
  - PCP role is to support process
  - Want Genomics help with current management
- Returning results increased clinician support of MyCode

ClinGen Consent & Disclosure Recommendatio Working Group

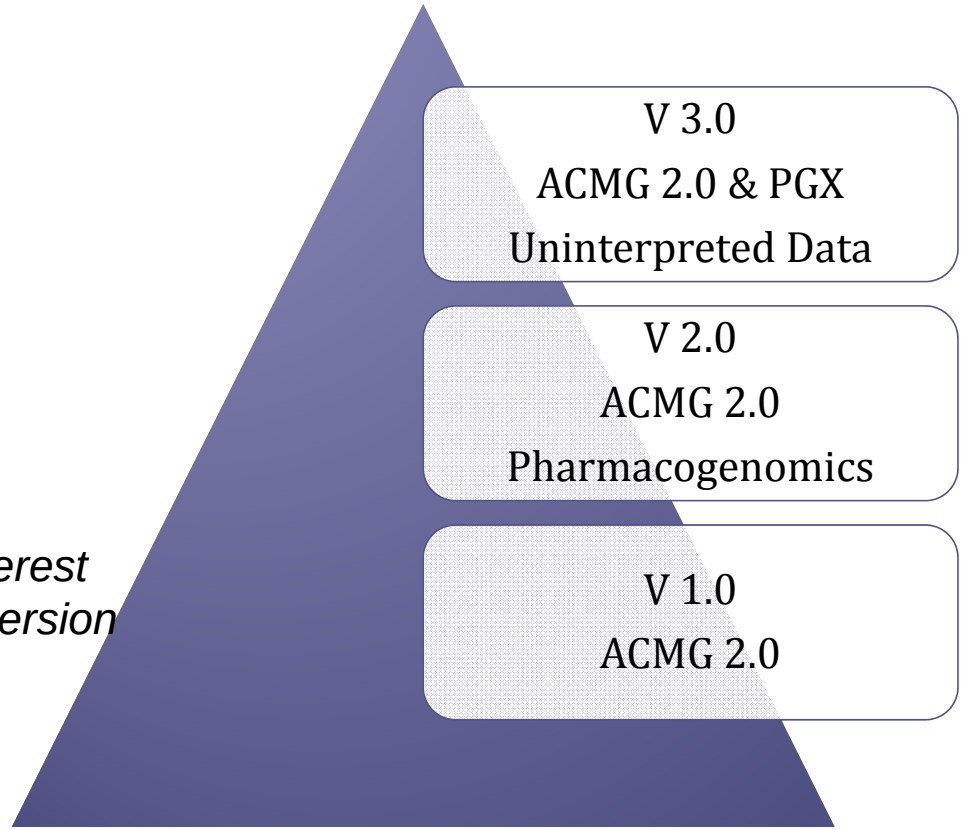


ACMG SFv2.0 gene recommendations completed

All of Us - Thoughts On What To Return

- ACMG 2.0 (59 genes)
  - Manageable numbers – 3.5 – 4%
  - “High Value” – medically actionable
  - GC community familiar
  - Commercial lab support – education materials
- Pharmacogenomics
  - Most participants will receive result (100%)
  - More value for older participants
  - Return with educational materials & limited GC and pharmacist support
- “Uninterpreted Data”
  - Process / Format

All of Us Results Sharing Versions



Confirm interest with each version

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