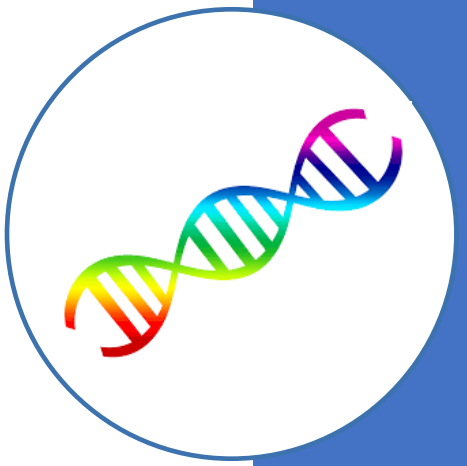
Genomic Clinical Implementation for Precision Medicine



HCSRN Scientific Data Resources Forum

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Hawaii Permanente Medical Group

Kaiser Permanente, Hawaii Region

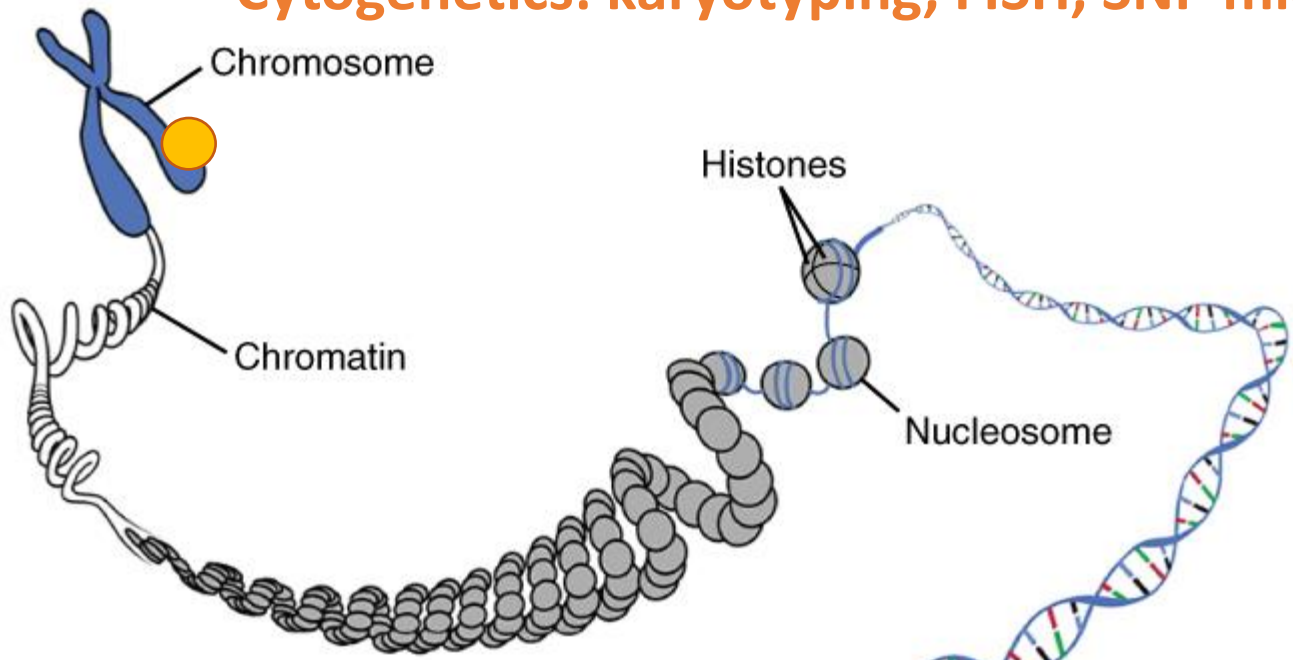
Overview

- Describe genomics in healthcare and actionable diseases
- Genetic testing in the Virtual Data Warehouse (VDW)
- Integrating clinical genetic testing and research genomics
- Improving access to genetic health services

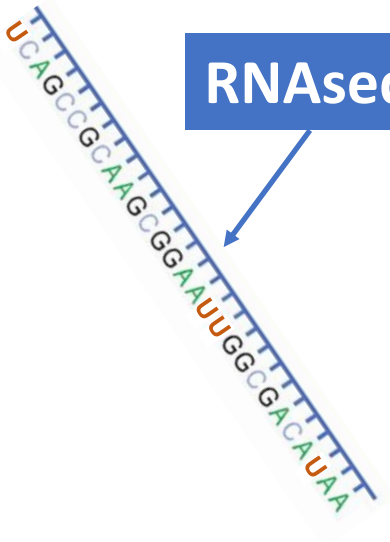
Disclosures: No commercial relationships to disclose

Genomic Tools

Cytogenetics: karyotyping, FISH, SNP microarray



RNAseq



Exons (2%)

ATGACGGATCAGCCGCAAGCGGAATTGGCGACATAA

TACTGCCTAGTCGGCGTTCGCCTTAACCGCTGTATT

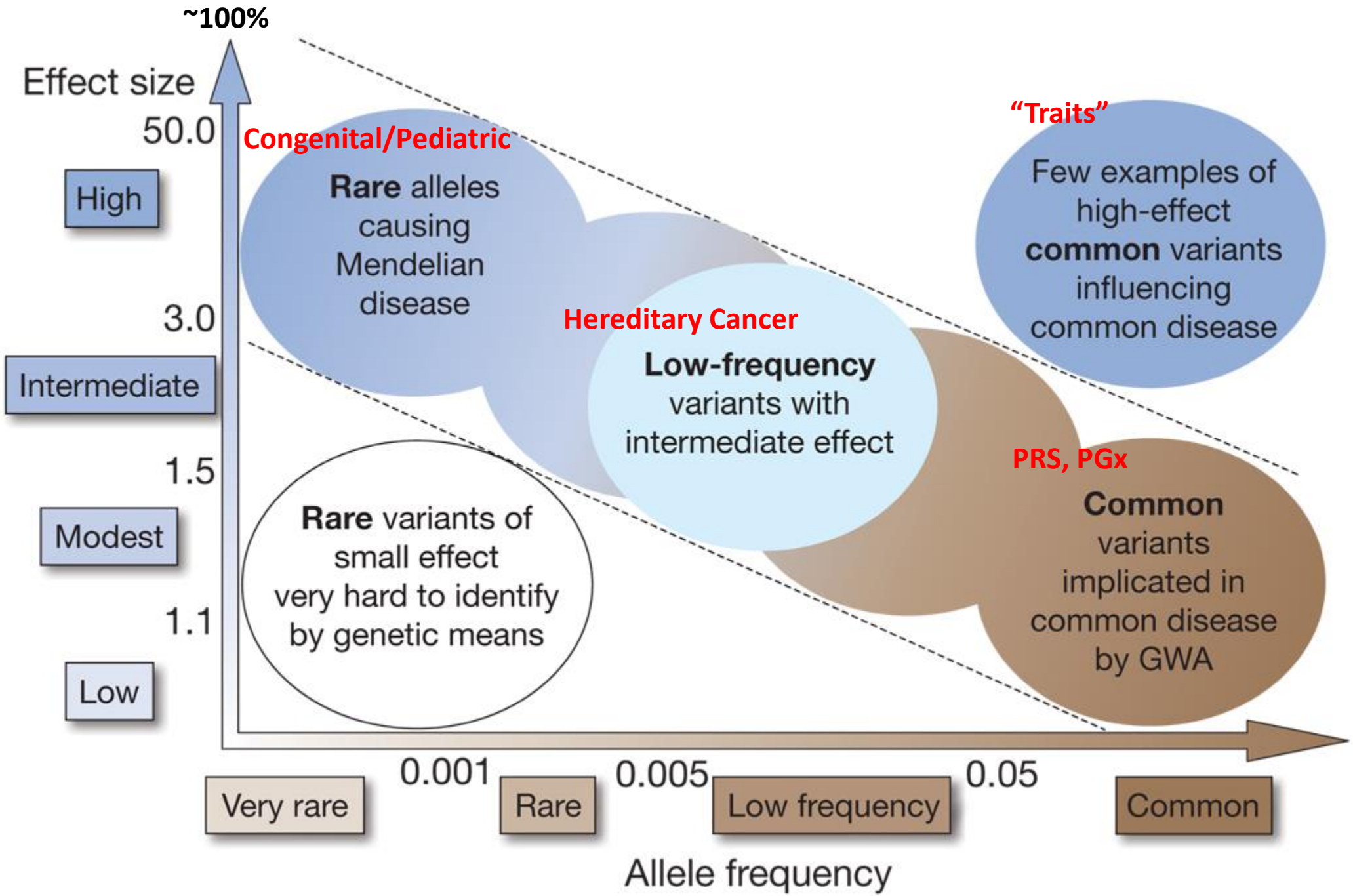
Sanger sequencing

Molecular Genetics

Panels

Exome

Genome


~100%
Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Congenital/Pediatric
Rare alleles causing Mendelian disease
"Traits"
Few examples of high-effect common variants influencing common disease
Hereditary Cancer
Low-frequency variants with intermediate effect
PRS, PGx
Common variants implicated in common disease by GWA
Rare variants of small effect very hard to identify by genetic means
0.001
0.005
0.05
Very rare
Rare
Low frequency
Common
Allele frequency

Clinical Sequencing Options

- **By Single Gene or Locus**
  - Sanger, Next generation sequencing (NGS)
  - Usually for 1:1 gene:phenotype relationships (*RS1*, Blue Cone Monochromatism)

- **With/Without Deletion/Duplication**
  - RT-PCR, ddPCR, SNP array, CGH, MLPA, Sanger (XY)

- **NGS Panels (various custom capture methods)**
  - Locus heterogeneity (IRDs, maculopathies, albinism, MAC)
  - Deletion/duplication analysis performed informatically

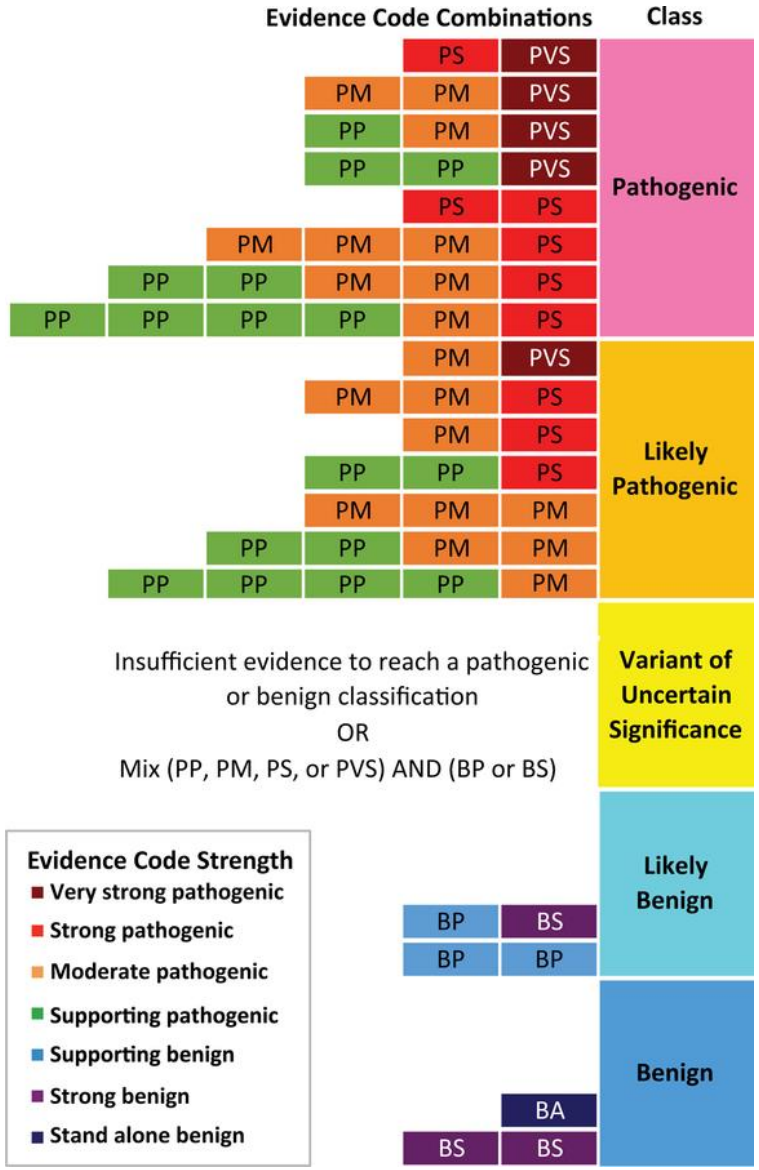
- **Clinical exome or genome sequencing**
  - **Emerging first-pass clinical testing for disorders with many causal genes**
  - Long-reads to sequence repetitive regions (*RPGR* orf15, XL opsin array)

Clinical variant interpretation – ACMG 2015 Guidelines

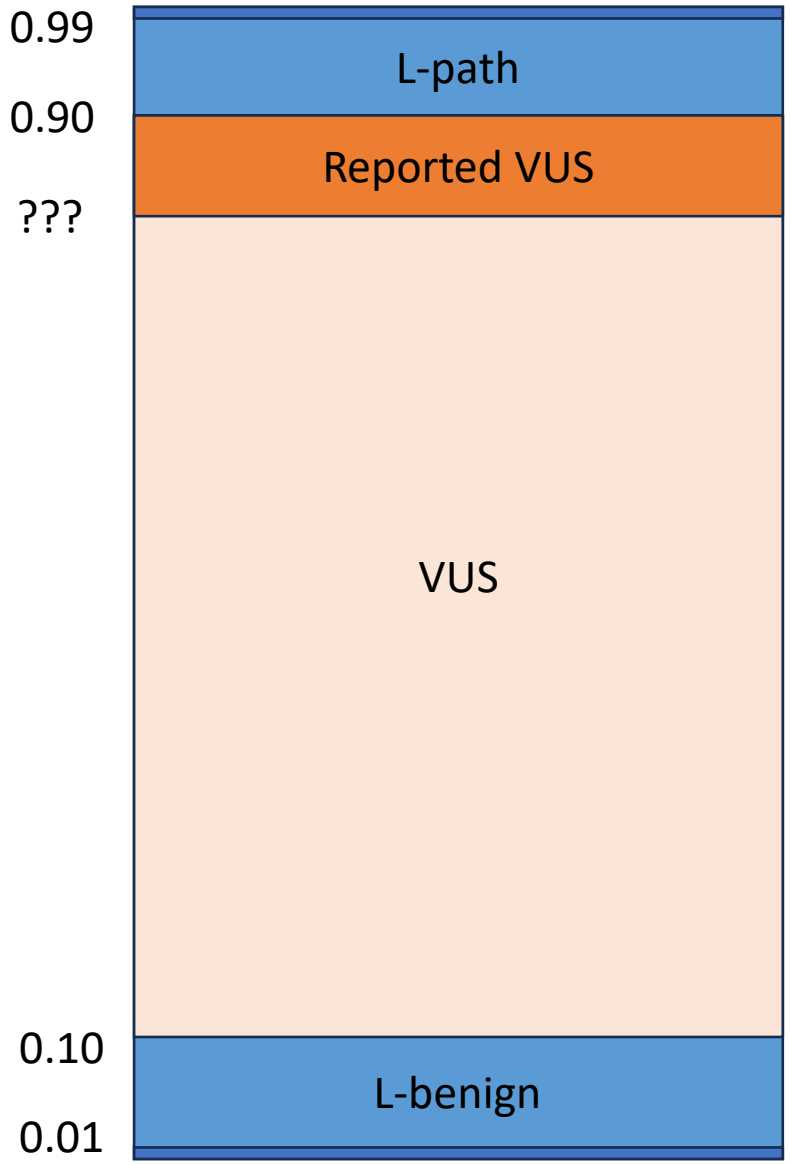
	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact *BP4* Missense when only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7* In-frame indels in repeat w/out known function *BP3*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		N ≤ 1/8 if 1 family N ≤ 1/4 if > 1 family	N ≤ 1/16 if 1 family N ≤ 1/8 if > 1 family	N ≤ 1/32 if 1 family N ≤ 1/16 if > 1 family	
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Richards et al, *Genetics in Medicine* (2015); Jarvik and Browning, *AJHG* (2016)

Variant Classes

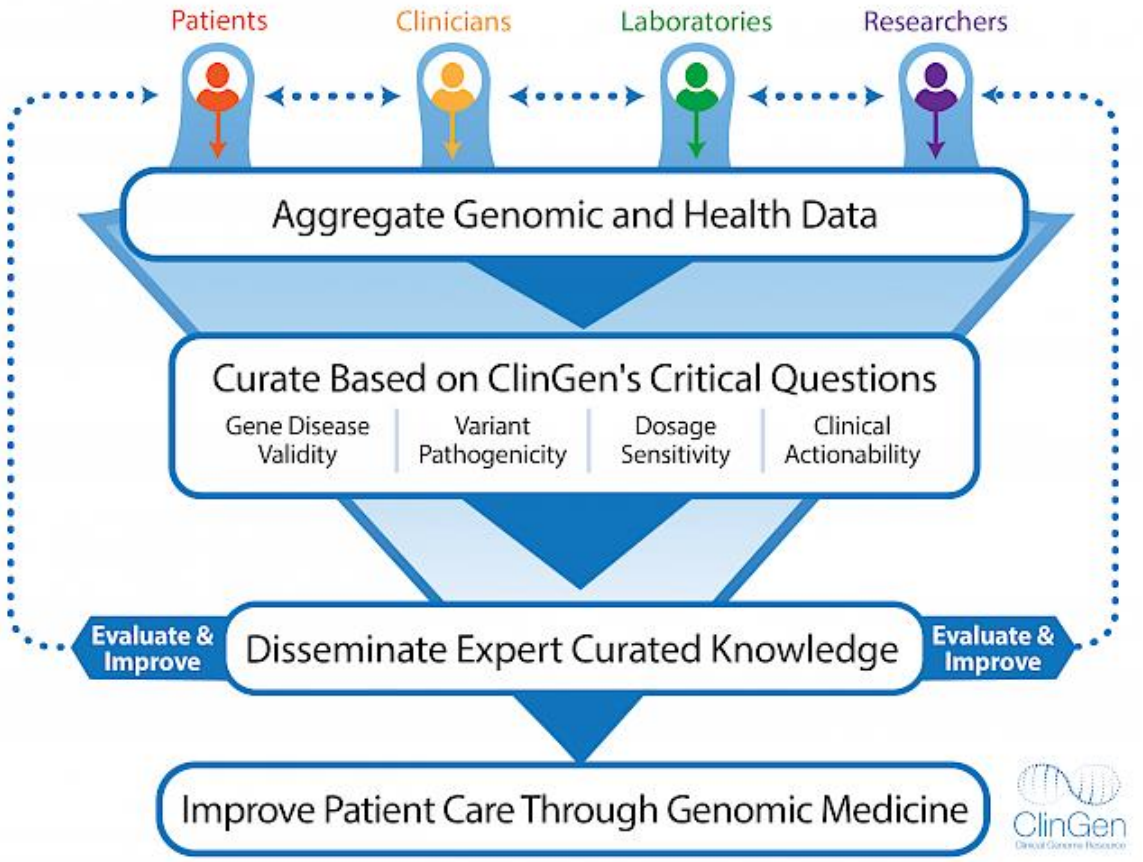


Class Probability



Brnich et al, Hum Mut 2018

Genomic Precision Medicine: ClinGen



- **Actionability: 84 genes (v3.4)**
- **Gene:disease association validity**
- **Gene-specific variant classification**

https://clinicalgenome.org/working-groups/clinical-domain/ocular-cdwg/

FDA Approval – *RPE65* – 2017

FDA NEWS RELEASE

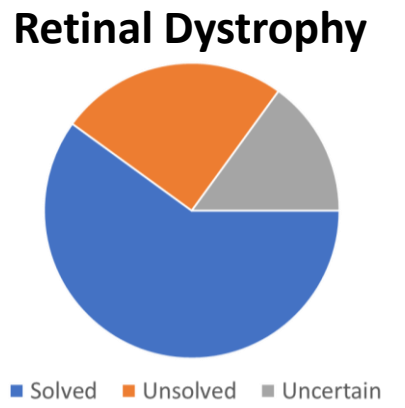
FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Share Tweet Linkedin Email Print

For Immediate Release: December 18, 2017

Español

The U.S. Food and Drug Administration today approved Luxturna (voretigene neparvovec-rzyl), a new gene therapy, to treat children and adult patients with an inherited form of vision loss that may result in blindness. Luxturna is the first directly administered gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene.



2021
***RPE65* added to the ACMGG 3.0 secondary findings genes**

***ABCA4* – Stargardt disease**
***CHM* – X-linked choroideremia**
***CNGA3* – Achromatopsia**
***CNGB3* – Achromatopsia**
***GUCY2D* – Leber congenital amaurosis**
***MERTK* – Retinitis pigmentosa**
***MYO7A* – Usher syndrome**
***PDE6B* – Retinitis pigmentosa**
***RLBP1* – Retinitis pigmentosa**
***RPGR* – X-Linked RP**
***RPGRIP*1 – Leber congenital amaurosis**
***RS1* – X-linked retinoschisis**
***USH2A* – Usher syndrome (Dual vector, ASO)**
***CEP290* – Leber congenital amaurosis (ASO, CRISPR)**

Members of the ClinGen Ocular Clinical Domain Working Group

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A. Vincent
A. Weisman
P. von Nandelstadh
M. Vortruba
S. Waap
A. Drackley
N. Wagner

Over 222 Members | 60 Institutions | in 16 Countries

Special thanks to our expert panel funding partners:

- National Human Genome Research Institute
- National Eye Institute
- Janssen Pharmaceuticals – previous *RPGR* funding
- Foundation Fighting Blindness

ClinGen
Clinical Genome Resource

RPE65-related recessive retinopathy

Search results for rpe65

Previous *Showing **1** to **2** of **2** results* Next

retinitis pigmentosa 20 MONDO:0013425

http://purl.obolibrary.org/obo/MONDO_0013425

Ontology: Mondo Disease Ontology MONDO

Leber congenital amaurosis 2 MONDO:0008765

http://purl.obolibrary.org/obo/MONDO_0008765

Ontology: Mondo Disease Ontology MONDO

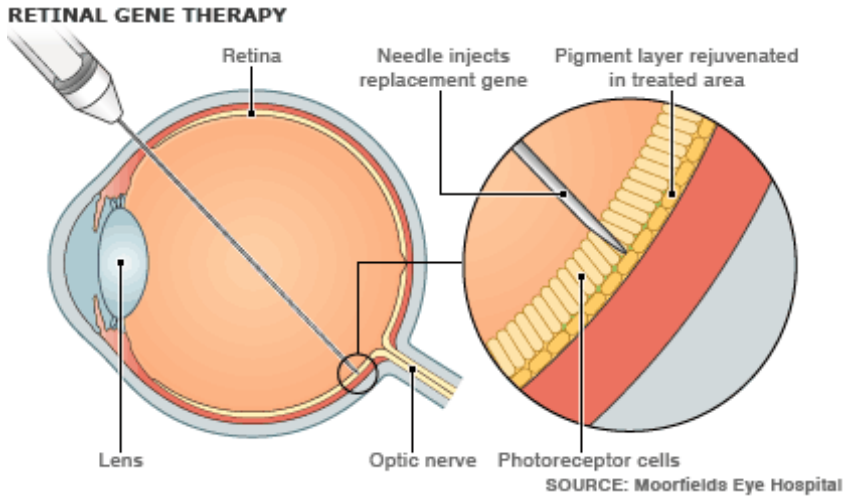
HGNC Approved Gene Symbol: RPE65

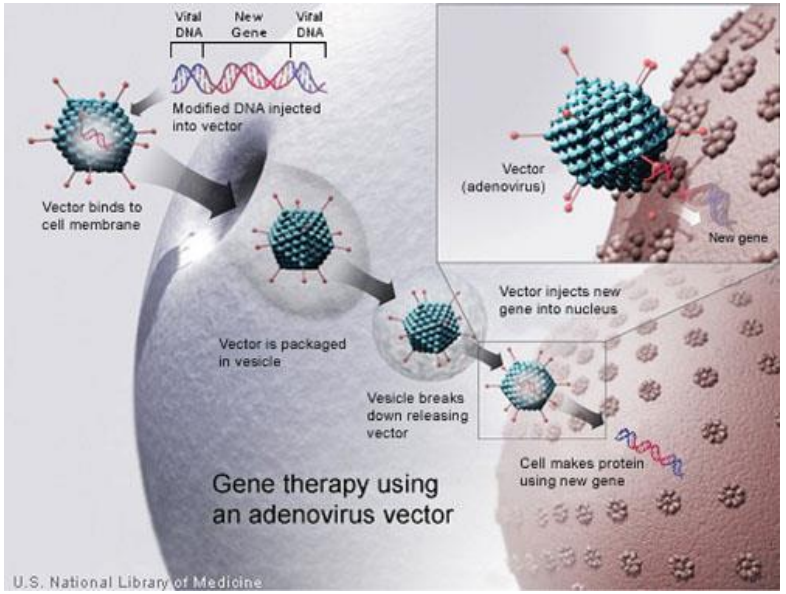
Cytogenetic location: 1p31.3 *Genomic coordinates (GRCh38): 1:68,428,821-68,450,321* (from NCBI)

Gene-Phenotype Relationships

View clinical synopses as a table

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
1p31.3	Leber congenital amaurosis 2	204100	AR	3
	Retinitis pigmentosa 20	613794	AR	3
	Retinitis pigmentosa 87 with choroidal involvement	618697	AD	3





FDA-approved *RPE65* variant classifications (ClinVar)

Classification type
- ☐ Germline (15)
- ☐ Somatic (0)

Germline classification
- ☐ Conflicting classifications (0)
- ☐ Benign (6)
- ☐ Likely benign (0)
- ☐ Uncertain significance (0)
- ☐ Likely pathogenic (0)
- ☐ Pathogenic (9)

Molecular consequence
- ☐ Frameshift (3)
- ☐ Missense (4)
- ☐ Nonsense (2)
- ☐ Splice site (3)
- ☐ ncRNA (0)
- ☐ Near gene (0)
- ☐ UTR (0)

Variation type
- ☐ Deletion (1)
- ☐ Duplication (2)
- ☐ Indel (0)
- ☐ Insertion (2)
- ☐ Single nucleotide (12)

Variation size
- ☐ Short variant (< 50 bps) (15)
- ☐ Structural variant (>= 50 bps) (0)

Variant length
- ☐ < 1kb, single gene (15)
- ☐ > 1kb, single gene (0)
- ☐ > 1kb, multiple genes (0)

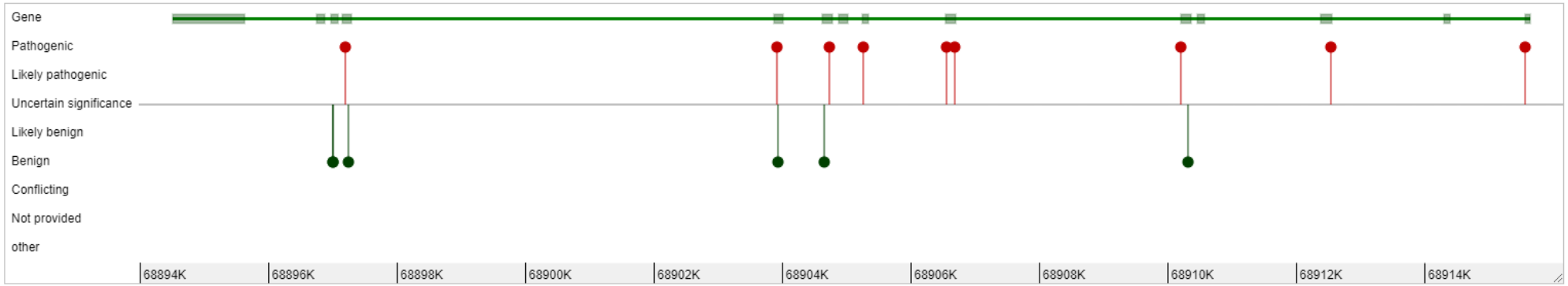
Review status clear
- ☐ Practice guideline (0)
- ☑ Expert panel (15)
- ☐ Multiple submitters (0)
- ☐ Single submitter (0)
- ☐ At least one star (15)
- ☐ Conflicting classifications (0)

Clear all

Show additional filters

Graphical view of search results

▶ GRCh37



Search results

Display options ▾ Sort by Relevance ▾ Download ▾ Items: 15

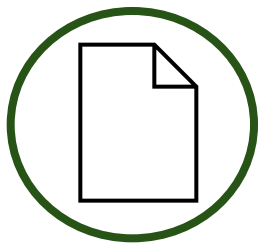
ⓘ Filters activated: Expert panel. Clear all to show 800 items.

Variation	Gene (Protein Change)	Type (Consequence)	Condition	Classification, Review status
NM_000329.3(RPE65):c.496-1G>A	RPE65	Single nucleotide variant (splice acceptor variant)	RPE65-related recessive retinopathy	G Pathogenic ★★★ FDA Recognized database
NM_000329.3(RPE65):c.886dup (p.Arg296fs)	RPE65 (R296fs)	Duplication (frameshift variant)	RPE65-related recessive retinopathy	G Pathogenic ★★★ FDA Recognized database
NM_000329.3(RPE65):c.1302G>A (p.Ala434=)	RPE65	Single nucleotide variant (synonymous variant)	RPE65-related recessive retinopathy	G Benign ★★★ FDA Recognized database
NM_000329.3(RPE65):c.615_616del (p.Ile206fs)	RPE65 (I206fs)	Deletion (frameshift variant)	RPE65-related recessive retinopathy	G Pathogenic ★★★ FDA Recognized database
NM_000329.3(RPE65):c.495+1dup	RPE65 (V166fs)	Duplication (frameshift variant +1 more)	RPE65-related recessive retinopathy	G Pathogenic ★★★ FDA Recognized database
NM_000329.3(RPE65):c.1087C>A (p.Pro363Thr)	RPE65 (P363T)	Single nucleotide variant (missense variant)	RPE65-related recessive retinopathy	G Pathogenic ★★★ FDA Recognized database

Overview

- Describe genomics in healthcare and actionable diseases
- **Genetic testing in the Virtual Data Warehouse (VDW)**
- Integrating clinical genetic testing and research genomics
- Improving access to genetic health services

CESR VDW MM Data Flow

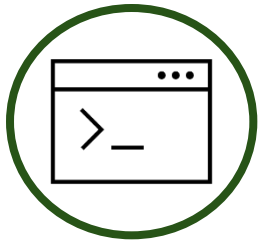


Laboratory Vendors

- Securely send discrete test result data as text files to KPIT

National KP IT

- Loads vendor data into central database
- Provides research sites access to regional views

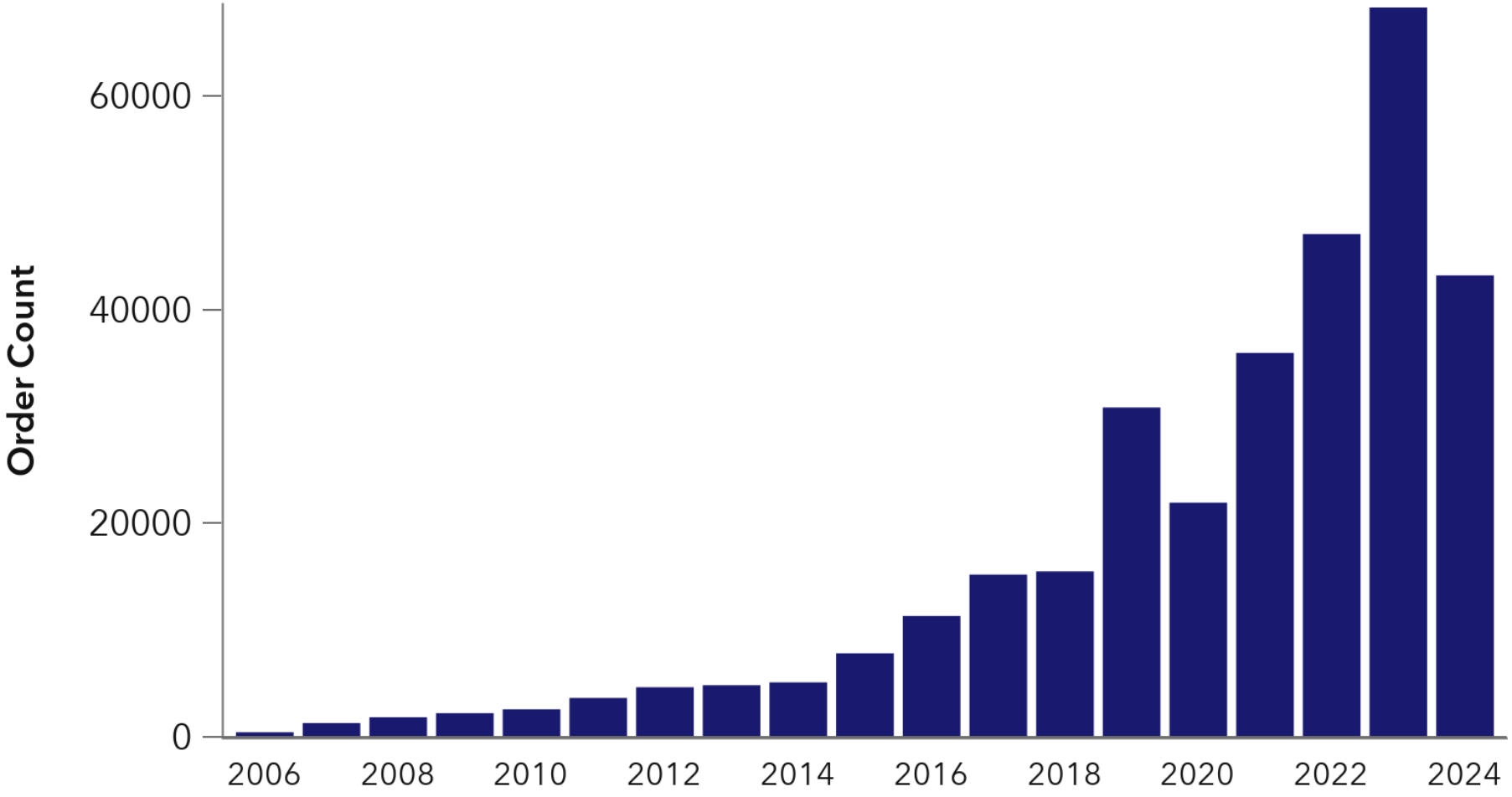


KP Research Sites

- Read data from KPIT database
- Standardize data using CESR scripts
- Load data into regional VDW

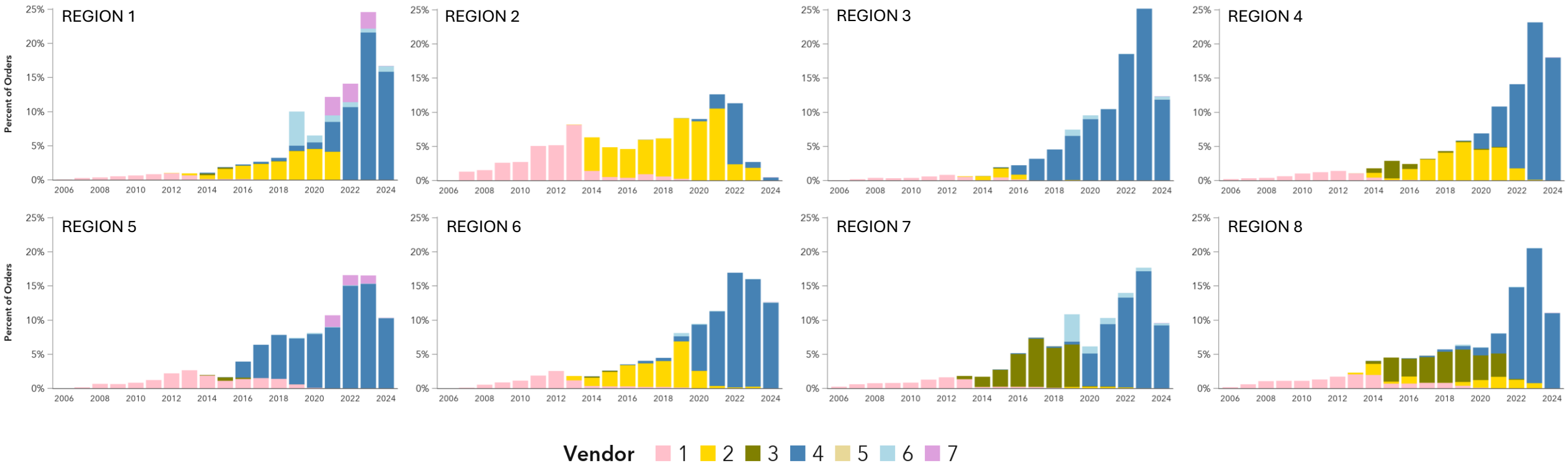
CESR
Kaiser Permanente Center for Effectiveness & Safety Research

Overall order count at 8 KP regions between years 2006-mid 2024 (July 2024)

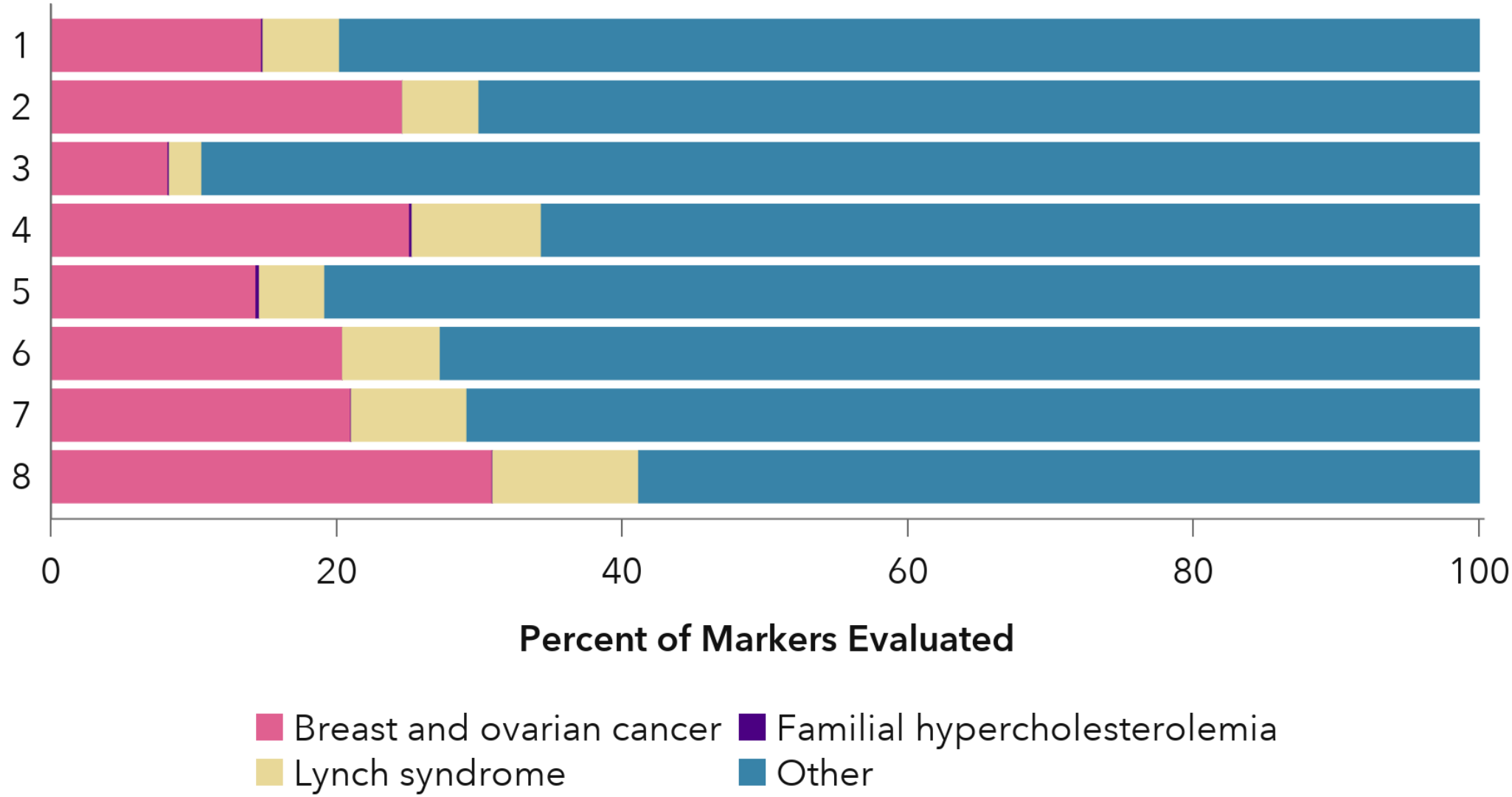


Counts	CESR (2006-2024)
Unique Orders	323,664
Unique participants	n/a
Total genes tested	14,999,424
Total variants reported	226,533

Vendor makeup of total orders by KP region from 2016 to 2024

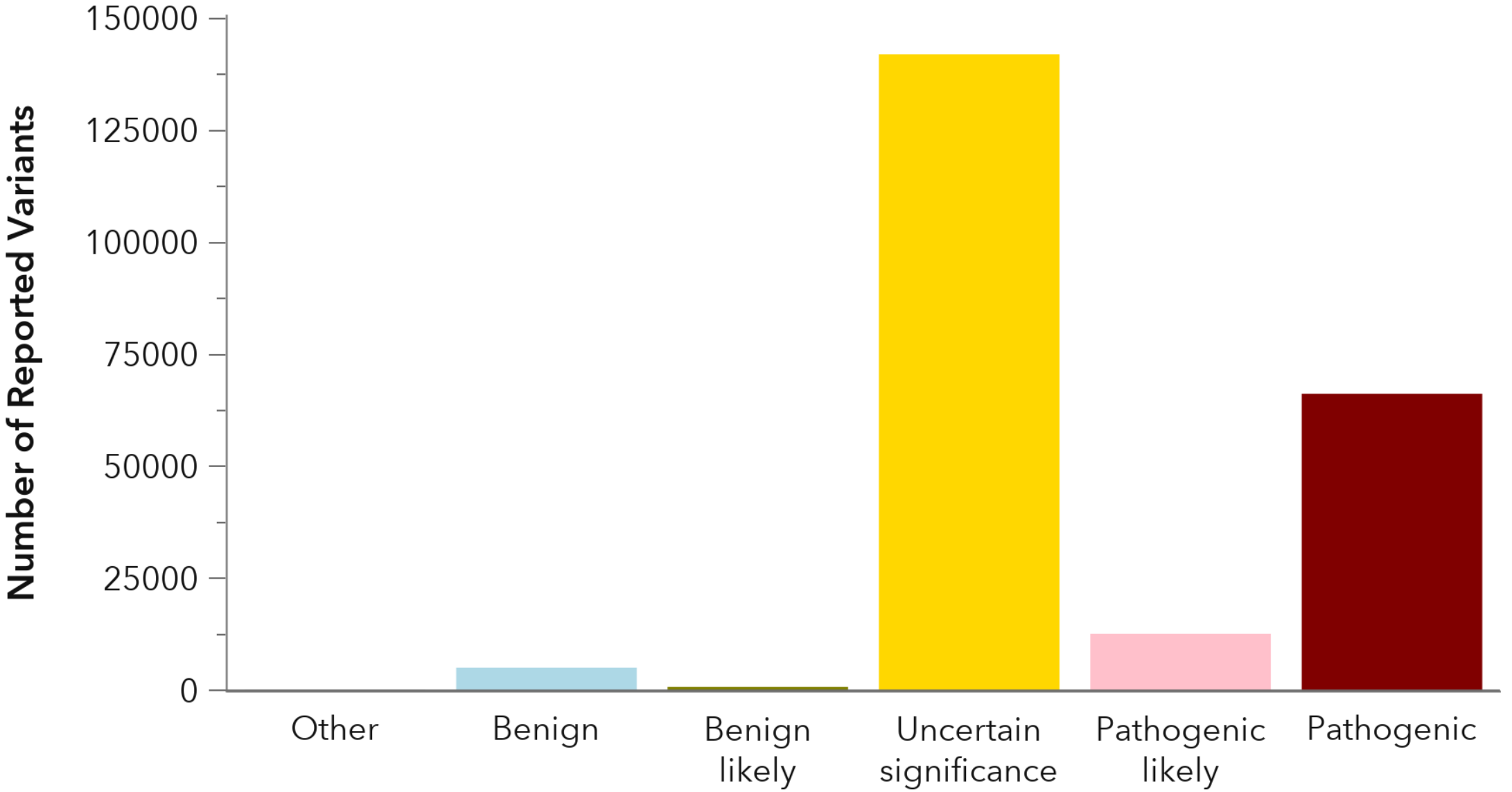


Markers evaluated by disease group



Breast and ovarian cancer markers: ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
Lynch syndrome markers: MLH1, MSH2, MSH6, PMS2, EPCAM
Familial hypercholesterolemia markers: LDLR, APOB, PCSK9

Total variants detected at 8 KP regions by classification 2016 –2024



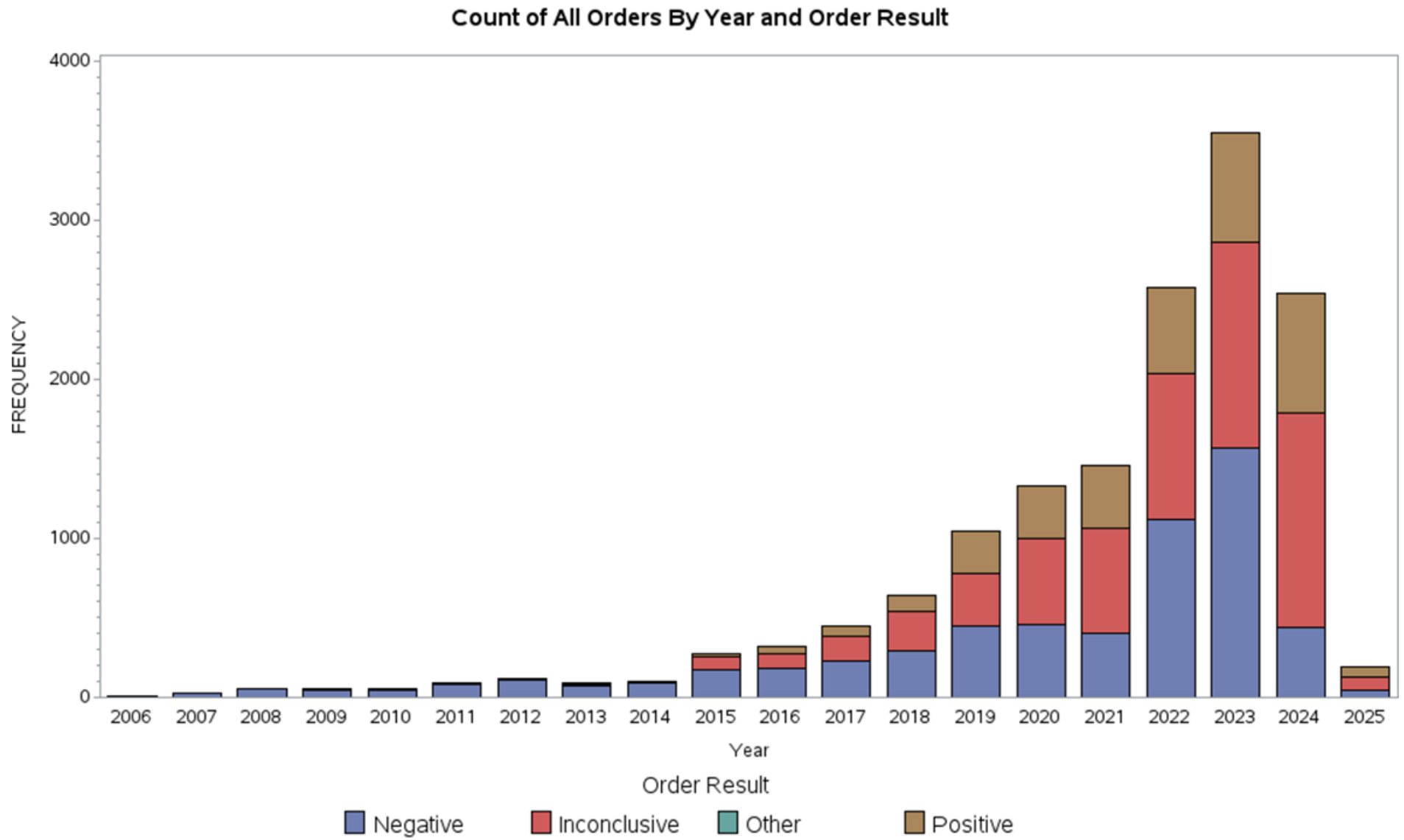
CESR VDW MM Table Format

	VENDOR	VENDOR PULL DATE	ACCOUNT NBR	SPECIMEN NBR	ORDERING PROV ID	ORDERING INST ZIP	RECEIVING PROV ID	RECEIVING INST ZIP	ORDER DATE	ORDER NAME	ORDER ID	MARKERS EVALUATED	CPT CODE	COLLECTION DATE	DISEASE ASSESSED	DISEASE ASSESSED CODING SYSTEM	RESULT DATE	MOST PATHOGENIC RESULT WITHIN ORDER	ORDER INTERPRETATION	ORDER INTERPRET VERSION	MARKER TYPE
VDWMRN_A	X		AQ	K	VDWPROVID_1					SCN9A ONLY	1	SCN9A						INCONCLUSIVE	MARKER HAS INCONCLUSIVE MUTATION	1	GM
VDWMRN_B	Y		AR	J	VDWPROVID_2					BREAST CANCER PANEL	2	BRCA1, BRCA2, CDH1, PTEN, STK11, TP53	81162, 81321, 81406		Z15.01, Z15.02	10		NEGATIVE		1	GM
VDWMRN_C	Z		AS	I	VDWPROVID_3					BRCA1&2	3	BRCA1,BRCA2						POSITIVE	AT LEAST 1 MARKER HAS PATHOGENIC MUTATION	1	GM

MRN	ORDER ID	RESULT DATE	MARKER	MARKER DESC	MOST PATHOGENIC MARKER CLASSIFICATION	MARKER INTERPRETATION	MARKER CODING SYSTEM	MARKER VERIFIED	MARKER INTERPRET VERSION	MARKER LOINC
VDWMRN_A	1		SCN9A	SODIUM VOLTAGE-GATED CHANNEL ALPHA SUBUNIT 9	UNCERTAINSIG	1 HETEROZYGOUS UNCERTAIN SIGNIFICANCE VARIANT FOUND IN SCN9A	HGNC	Y	1	
VDWMRN_B	2		BRCA1	BRCA1, DNA REPAIR ASSOCIATED	NEGATIVE		HGNC	Y	1	
VDWMRN_B	2		BRCA2	BRCA2, DNA REPAIR ASSOCIATED	NEGATIVE		HGNC	Y	1	
VDWMRN_B	2		CDH1	CADHERIN 1	NEGATIVE		HGNC	Y	1	
VDWMRN_B	2		PTEN	PHOSPHATASE AND TENSIN HOMOLOG	NEGATIVE		HGNC	Y	1	
VDWMRN_B	2		STK11	SERINE/THREONINE KINASE 11	NEGATIVE		HGNC	Y	1	
VDWMRN_B	2		TP53	TUMOR PROTEIN P53	NEGATIVE		HGNC	Y	1	
VDWMRN_C	3		BRCA1	BRCA1, DNA REPAIR ASSOCIATED	NEGATIVE		HGNC	Y	1	
VDWMRN_C	3		BRCA2	BRCA2, DNA REPAIR ASSOCIATED	PATHOGENIC	MARKER HAS PATHOGENIC MUTATION	HGNC	Y	1	

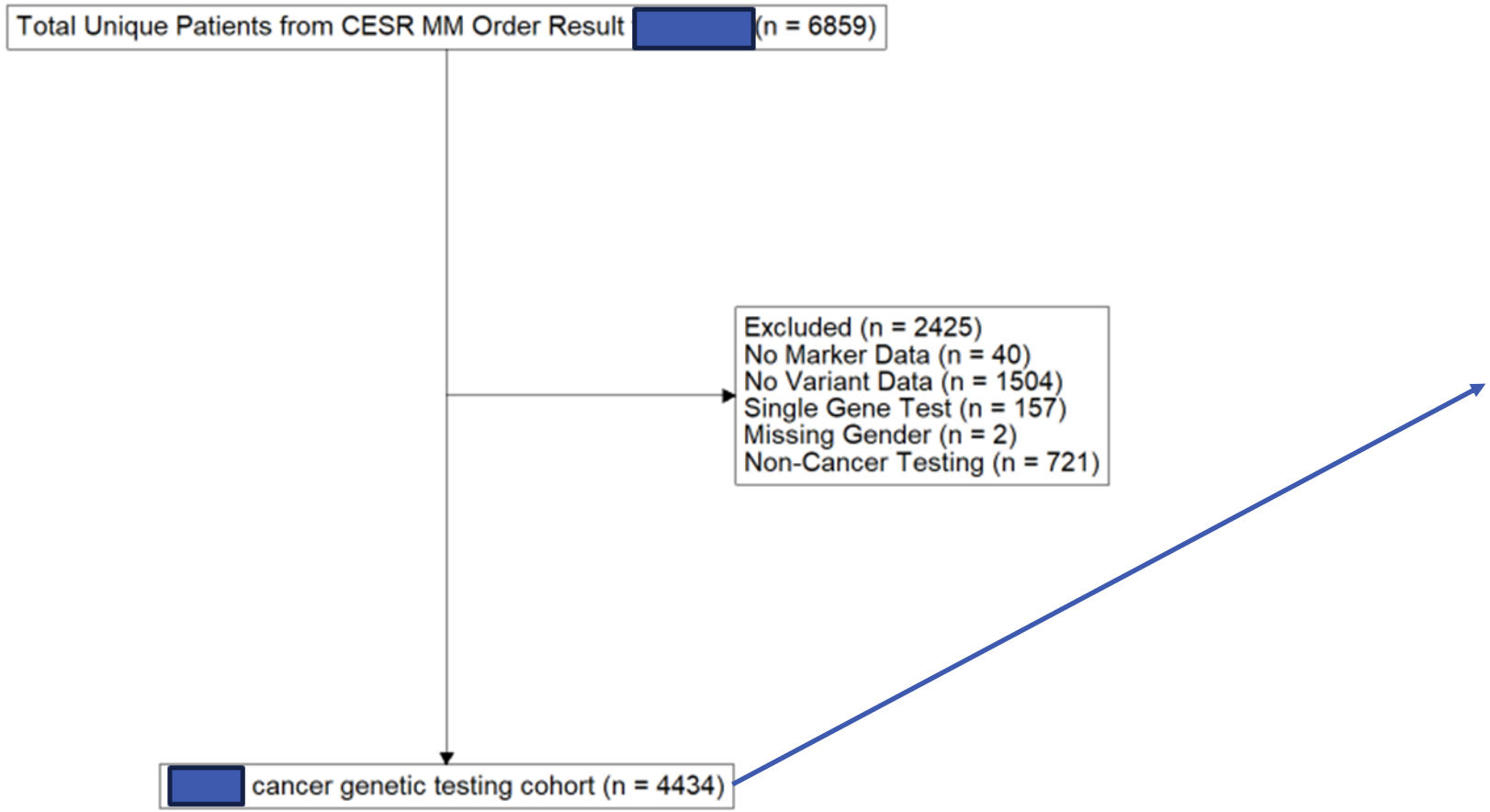
MRN	ORDER ID	RESULT DATE	MARKER	VARIANT	VARIANT CLASSIFICATION	VARIANT ALLELIC STATE	VARIANT GENOMIC SOURCE CLASS	VARIANT INTERPRETATION	VARIANT CODING SYSTEM	VARIANT ANALYSIS METHOD	VARIANT INTERPRET VERSION
VDWMRN_A	1		SCN9A	C.####C>A	UNCERTAINSIG	HETEROZYGOUS	GERMLINE	UNCERTAIN SIGNIFICANCE	HGVS	SEQUENCING	1
VDWMRN_C	3		BRCA2	C.###+#T>G	PATHOGENIC	HETEROZYGOUS	GERMLINE	PT HAS PATHOGENIC RESULT	HGVS	SEQUENCING	1
VDWMRN_C	3		BRCA2	C.####G>C	PATHLIKELY	HETEROZYGOUS	GERMLINE	RESULT IS LIKELY PATHOGENIC	HGVS	SEQUENCING	1

Regional data – Hawai’i



Draft Descriptive Tables for Improving Clinical Variant Classification for Cancer Genetic Testing

Data from 2015 to December 2024



4,434 Patients tested
10,855 Variants reported

variant_classification <fct>	n <int>
UNCERTAINSIG	8459
BENIGNLIKELY	201
PATHOGENIC	1952
PATHLIKELY	194
BENIGN	49

5 rows

Demographics – age, gender, race

Table 1. Patient Characteristics Among Patients in CESR MM [redacted] by Age Group

Characteristic	**Age 50+**, N = 2,670[1]	**Age <50**, N = 1,764[1]
Age as of 1st Result Date	65 (58, 72)	40 (35, 45)
Gender		
Female	2,012 (75%)	1,363 (77%)
Male	658 (25%)	401 (23%)
First Census Race		
Asian	990 (37%)	613 (35%)
White	913 (34%)	507 (29%)
Native Hawaiian / Pacific Islander	660 (25%)	435 (25%)
Unknown or Not Reported	64 (2.4%)	144 (8.2%)
American Indian / Alaskan Native	26 (1.0%)	29 (1.6%)
Black or African American	17 (0.6%)	36 (2.0%)

Differences in Clinical Utility Among Racial Groups

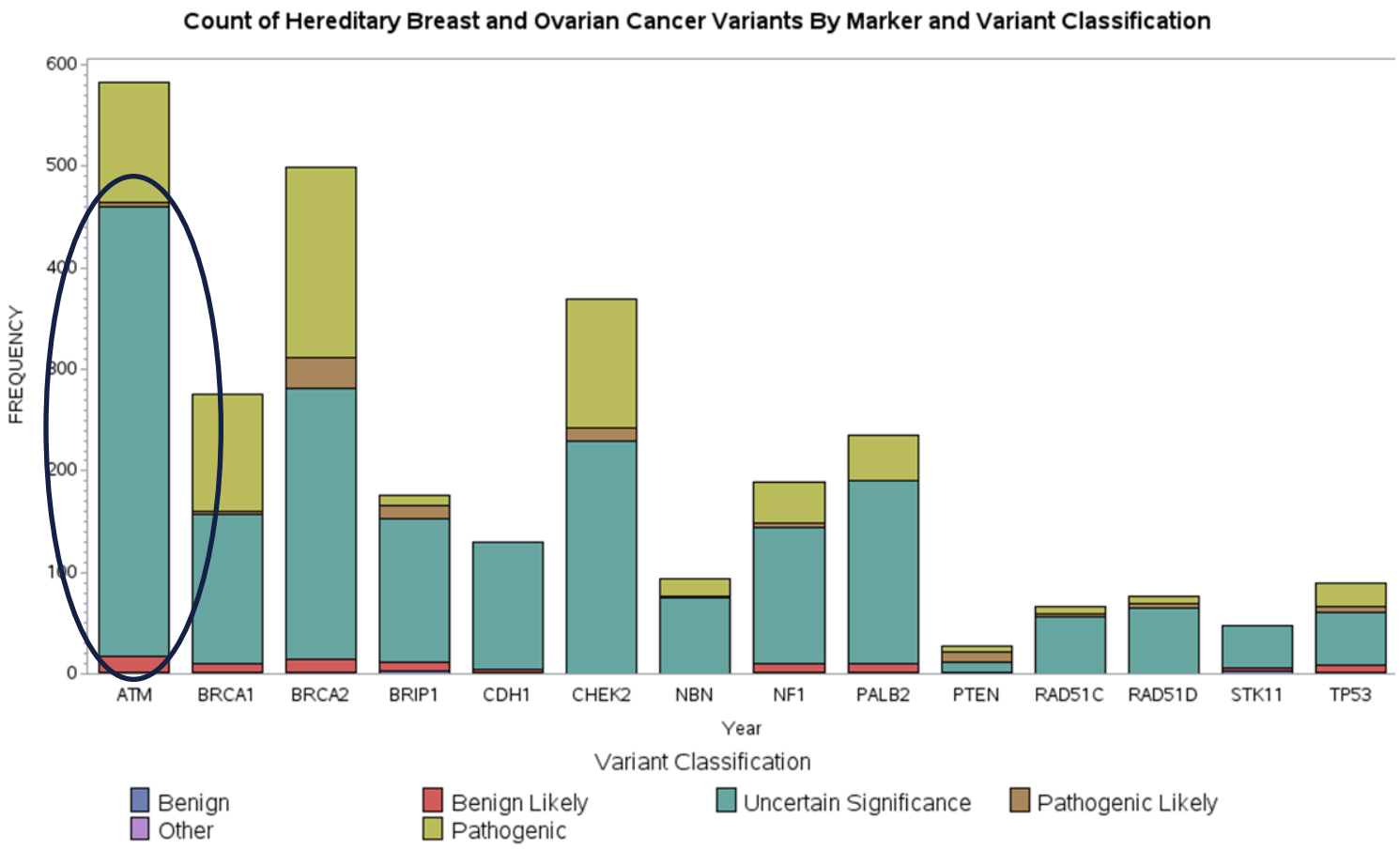
Rank order by First Census Race Diagnostic Testing Yield

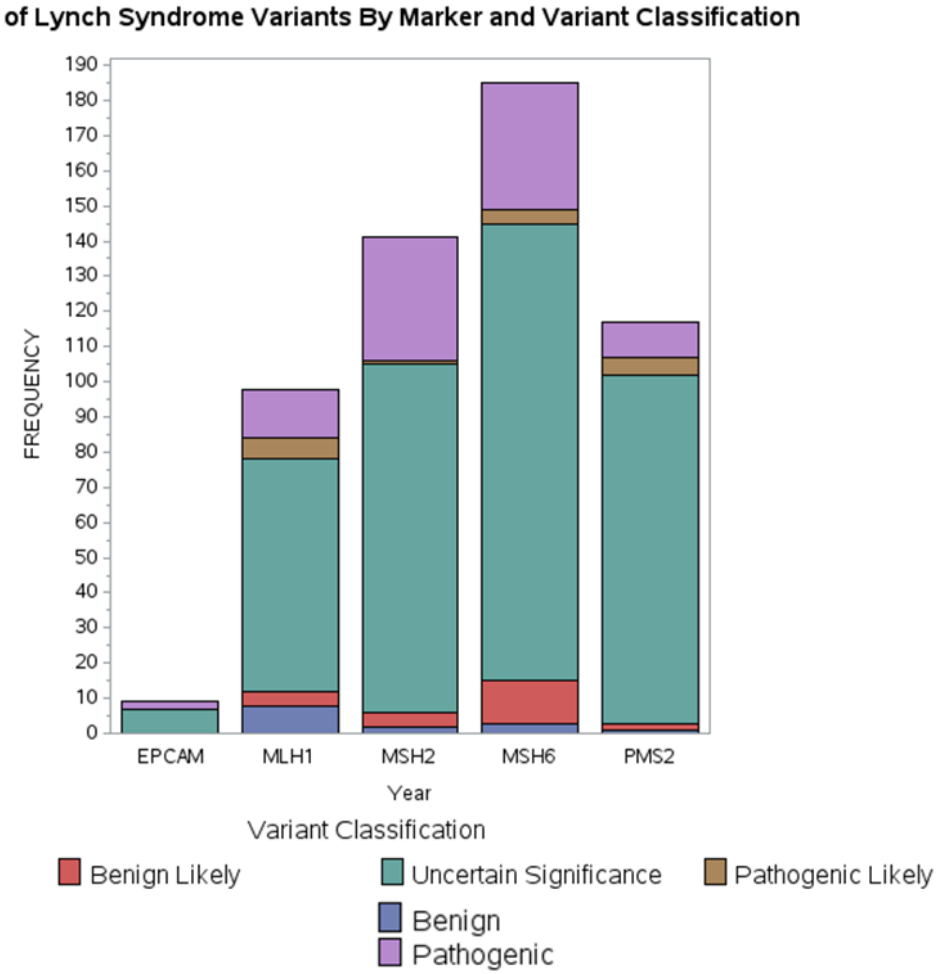
<u>Positive = Pathogenic/Likely Pathogenic</u>
White: 14.01% (n=1,420)
Asian: 7.80% (n= 1,603)
NHPI: 7.40% (n= 1,095)

Table 2. Cancer Types Among Patients in CESR MM from Invitae N=4,434

Cancer Types		
1	Family History Cancer,Family History Other Disease,Genetic Carrier Other Disease,Neoplasm Screening,Procreation Screening	395
2	Family History Cancer,Genetic Carrier Other Disease,Neoplasm Screening,Procreation Screening	381
3	Breast,Family History Cancer,Family History Other Disease,Genetic Carrier Other Disease,Neoplasm Screening,Personal History Cancer,Procreation Screening	189
4	Breast,Family History Cancer,Genetic Carrier Other Disease,Neoplasm Screening,Personal History Cancer,Procreation Screening	121
5	Genetic Carrier Other Disease,Neoplasm Screening,Procreation Screening	111
6	Genetic Carrier Other Disease,Procreation Screening	103
7	Breast,Family History Cancer,Family History Other Disease,Genetic Carrier Other Disease,Neoplasm Screening,Personal History Benign,Personal History Cancer,Procreation Screening	100
8	Family History Cancer,Family History Other Disease,Genetic Carrier Other Disease,Neoplasm Screening,Personal History Benign,Procreation Screening	90
9	Breast,Family History Cancer,Family History Other Disease,Genetic Carrier Other Disease,Neoplasm Screening,Procreation Screening	66
10	Family History Cancer,Family History Other Disease,Neoplasm Screening,Procreation Screening	60

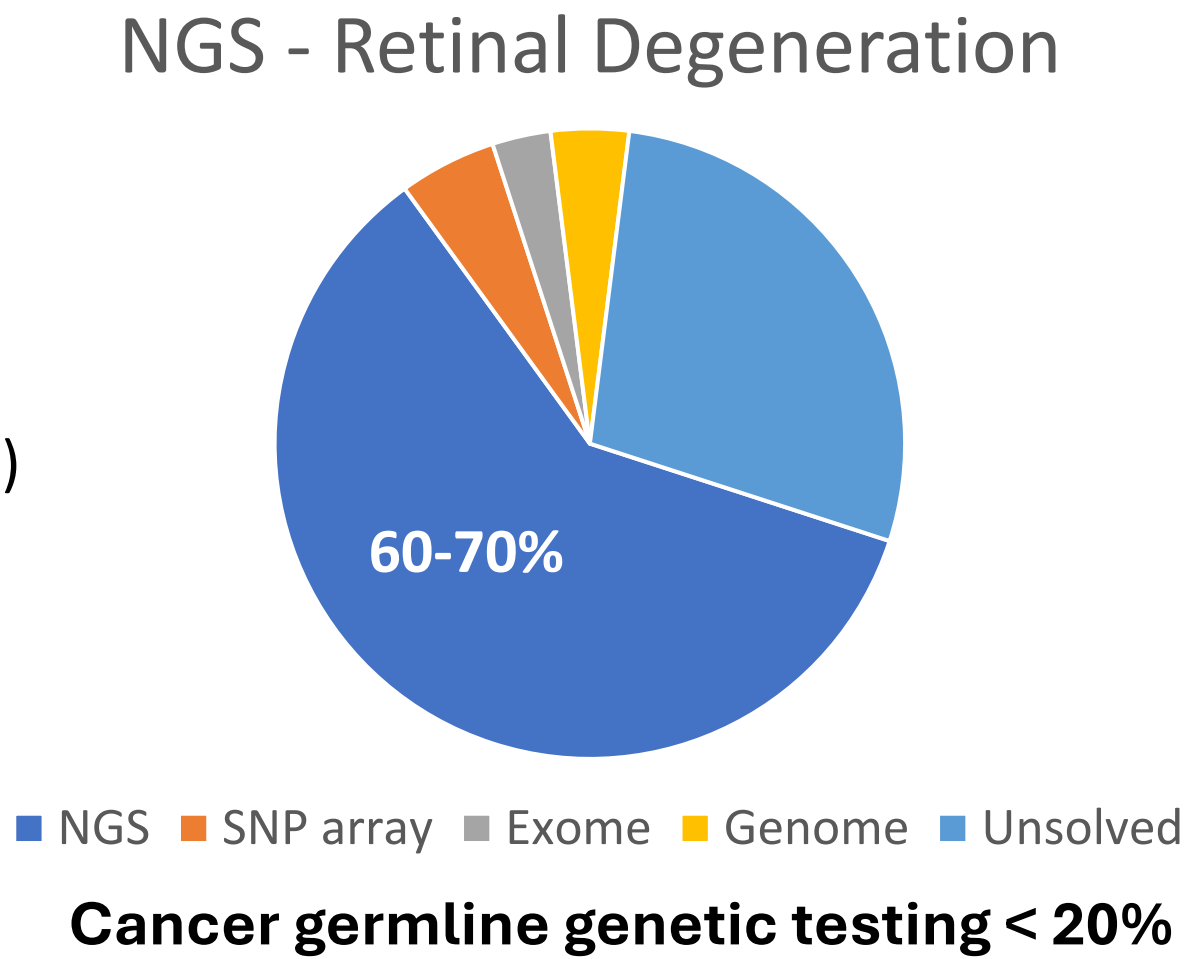
CDC Tier 1 cancer gene:variant distributions – Hawai'i





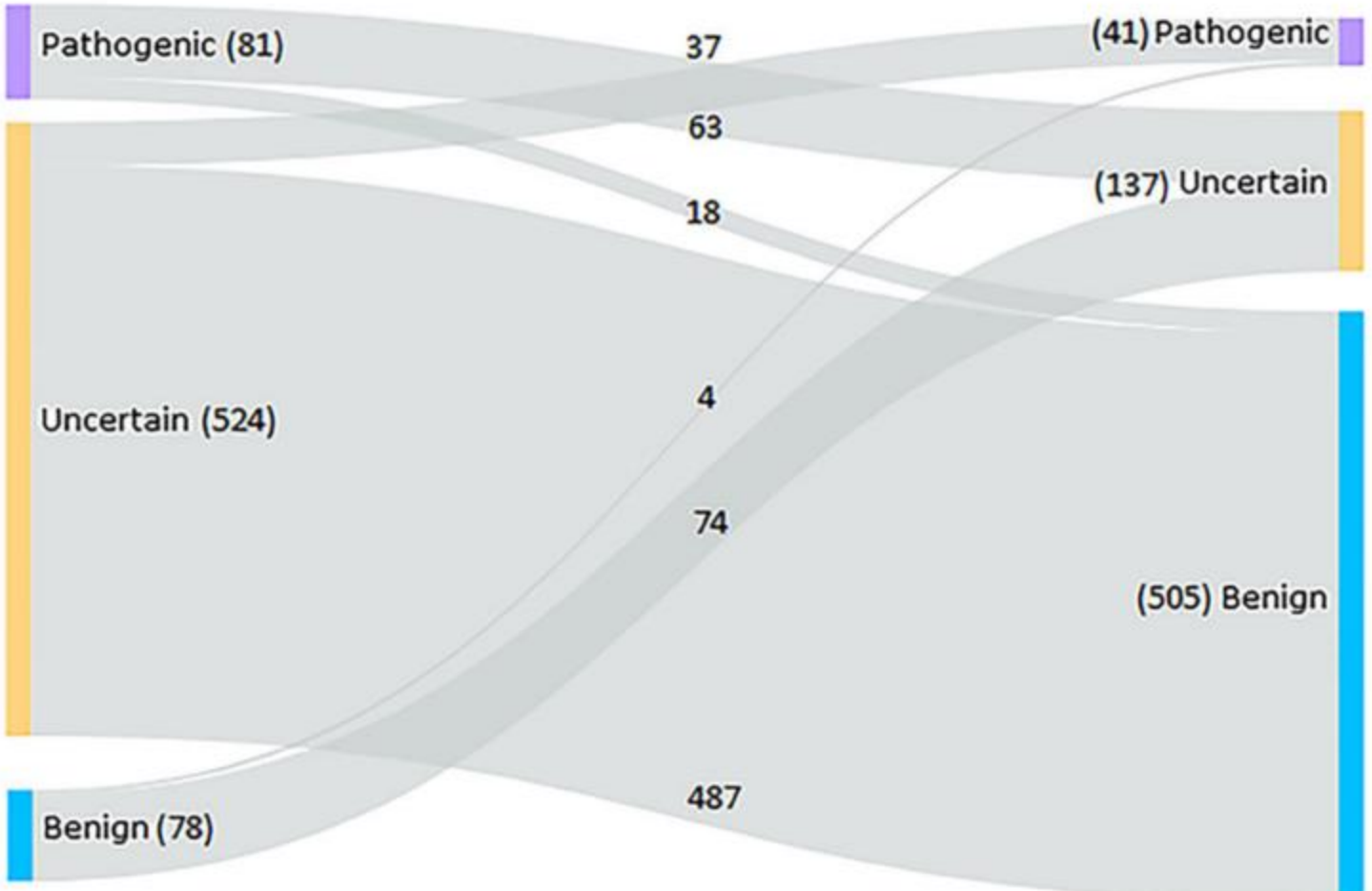
Variant Classification

- Variant association with “disease” status
  - Previous reports
    - Individual patients (ClinVar)
    - Functional studies
- Variant association with “healthy” status
  - Population databases (gnomAD/ExAC/etc)
    - Variant level (allele frequency)
    - Gene level (gene constraint metrics)
- *In silico* predictions



Cancer germline genetic testing < 20%

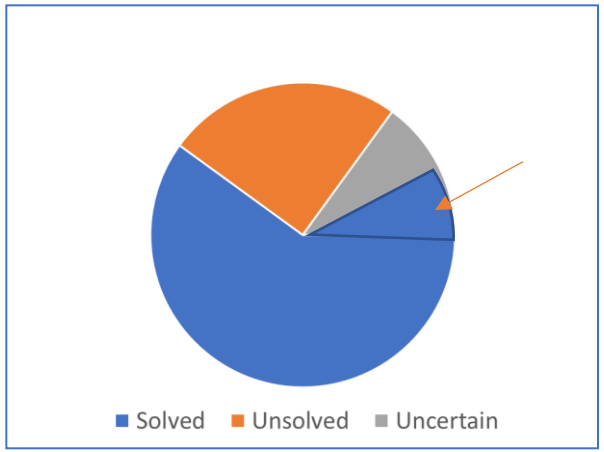
Variants tend to become benign over time and observations



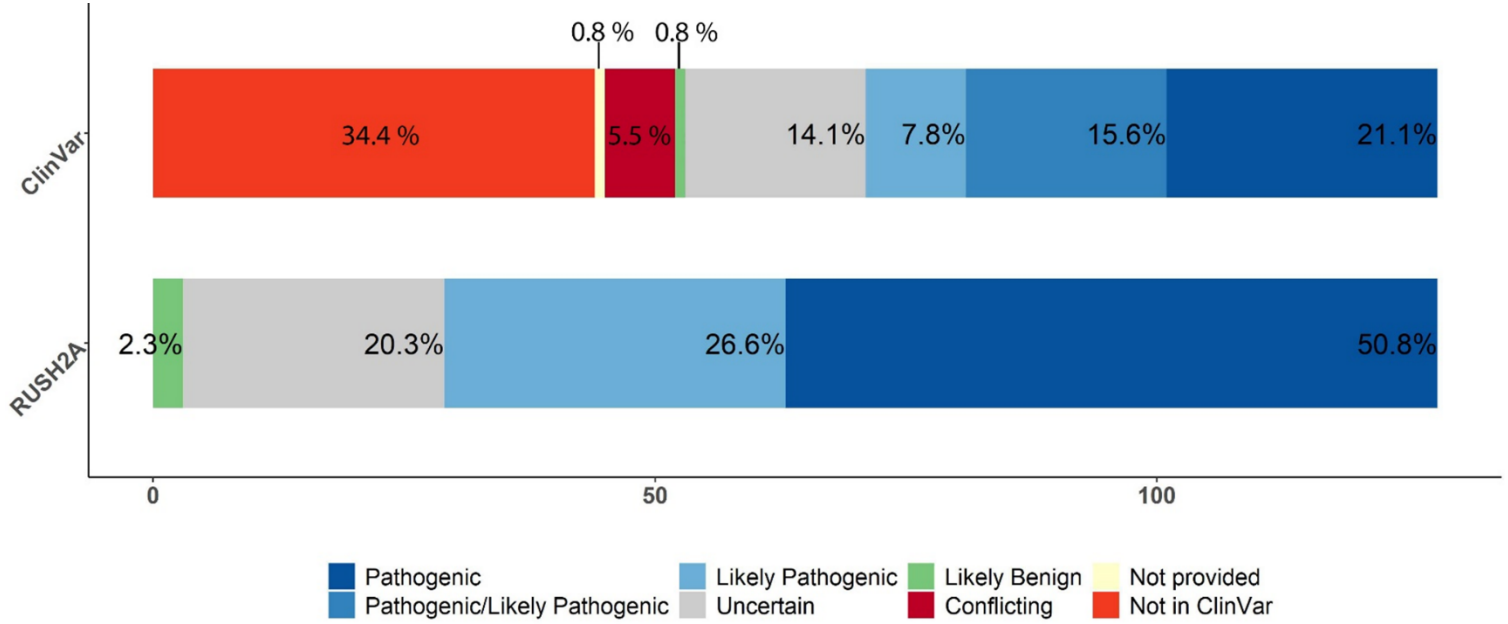
Time/Observations →

Goetz et al, AJMG C, 2020

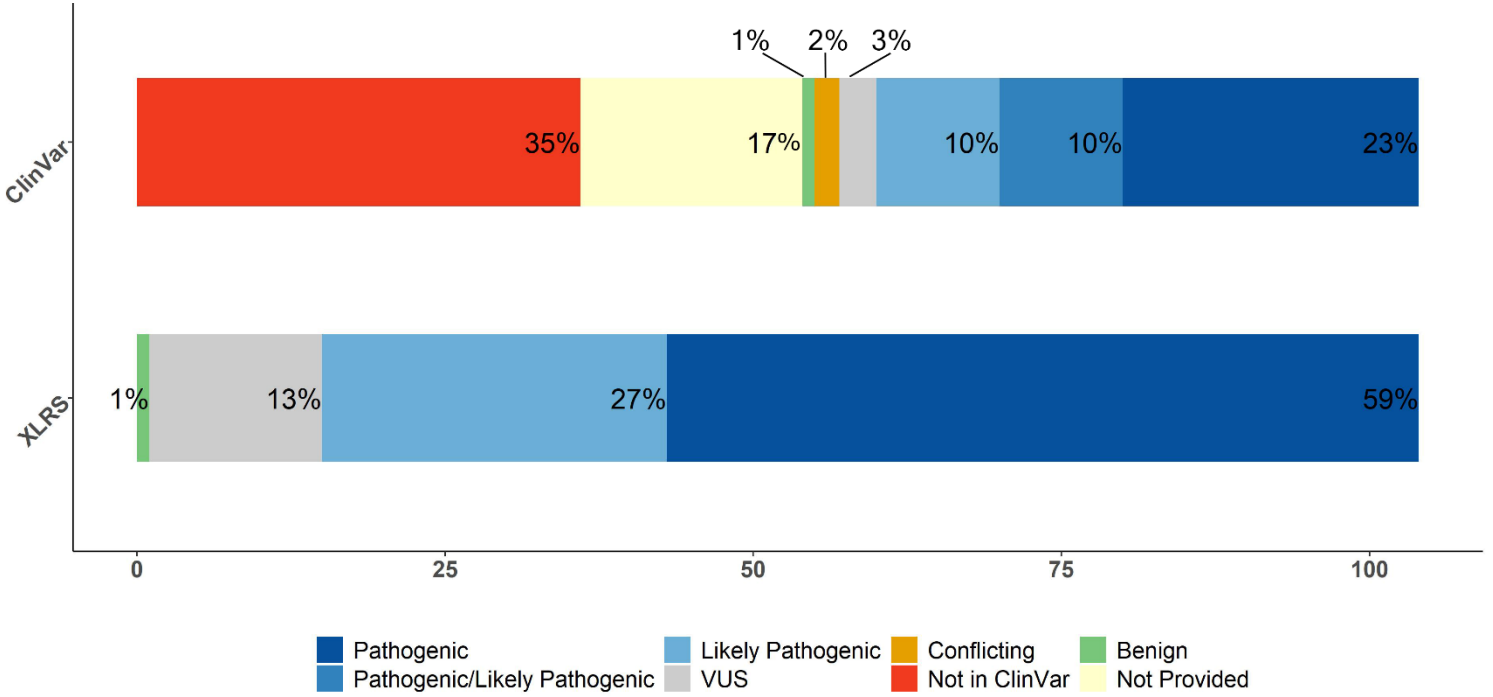
Consistency is good



USH2A

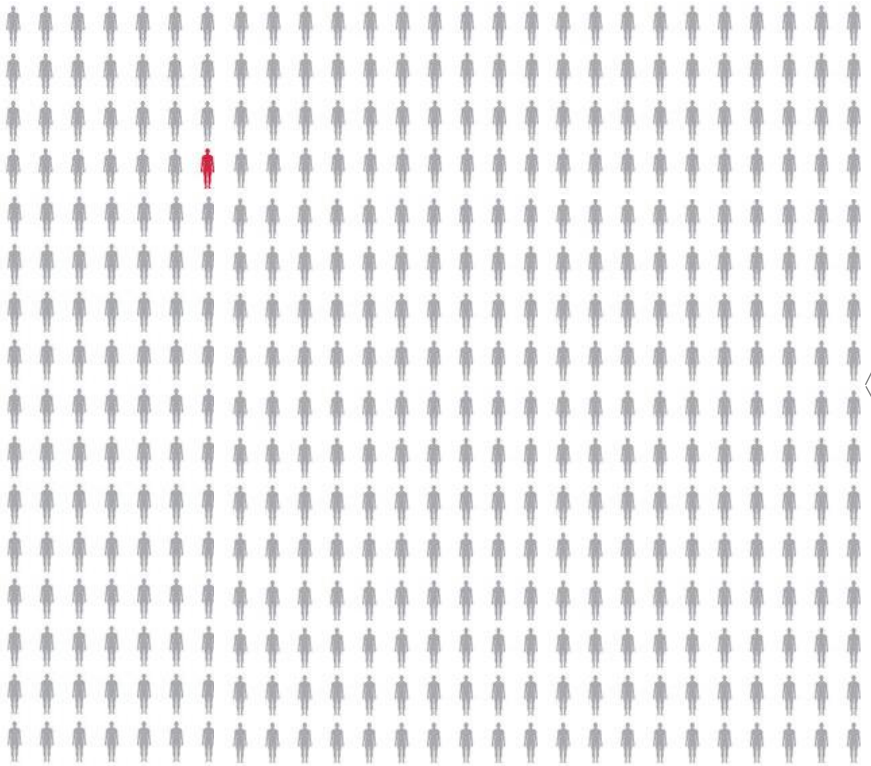


RS1

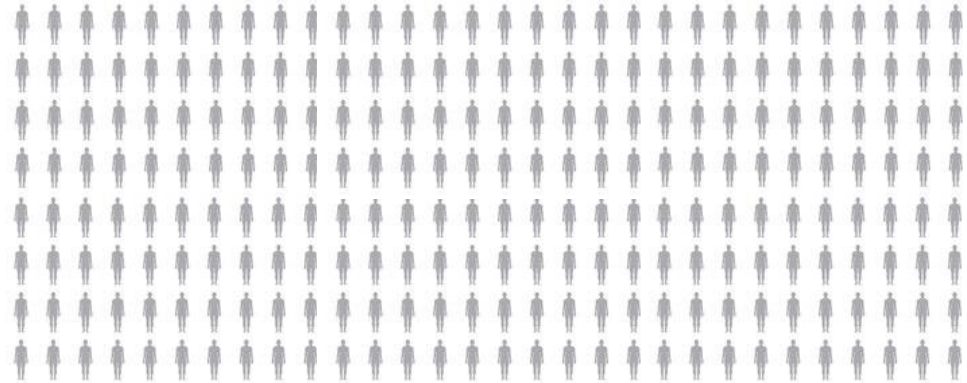


PRPH2: Reeves et al, *Human Mutation* (2020)
USH2A: Hufnagel et al, *Human Mutation* (2022)
RS1: Bender, Woo et al, *Genes* (2022)
PNPLA6: Liu et al, *Brain* (2024)
FEVR: Tuncay et al, *IOVS* (2025)
IRDs in African-Americans: Abuzaitoun et al (2024)

General Population (Rare Disease)



gnomAD/ExAC



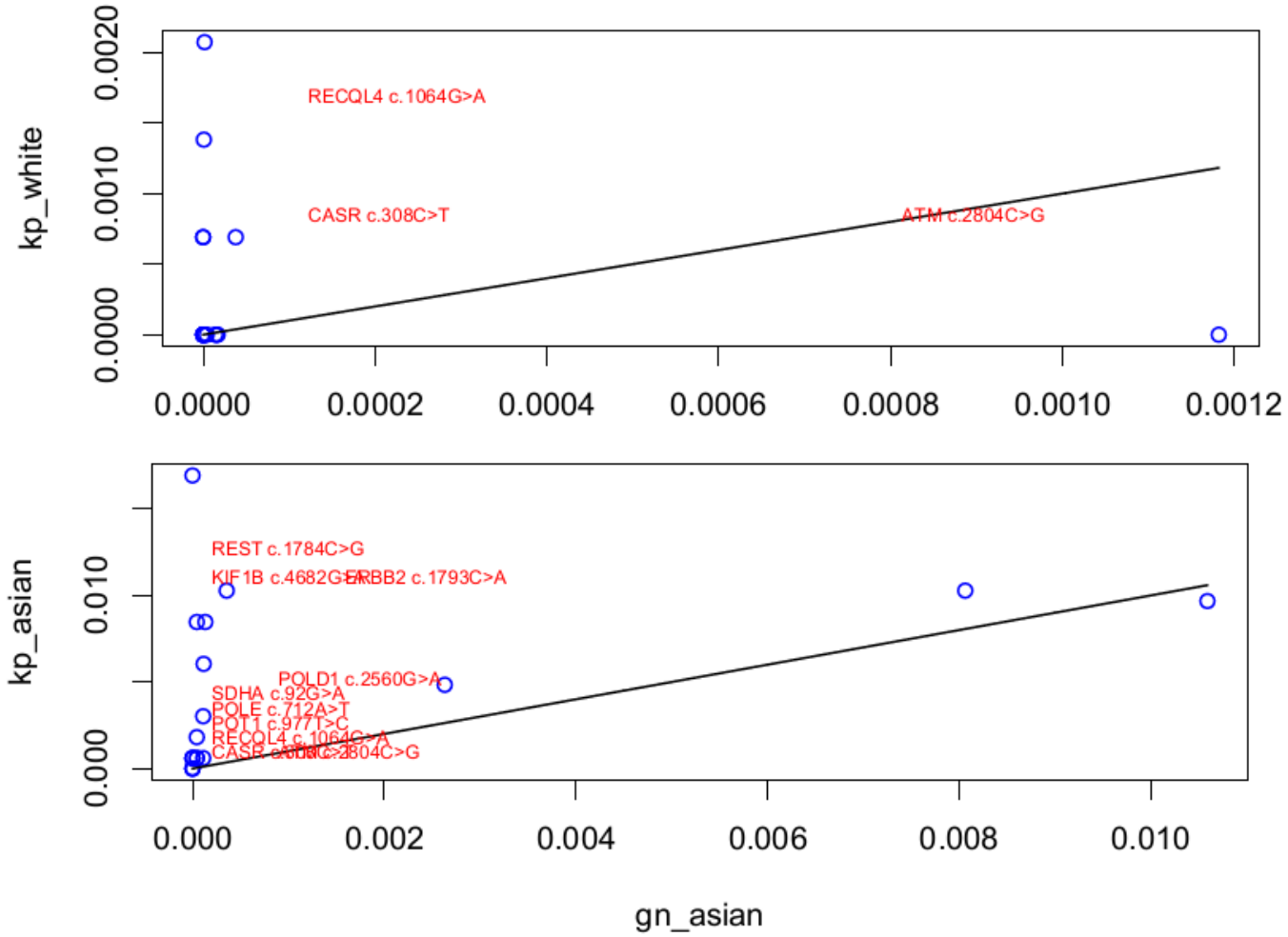
Breast Cancer

GENE
Phenotype
Group

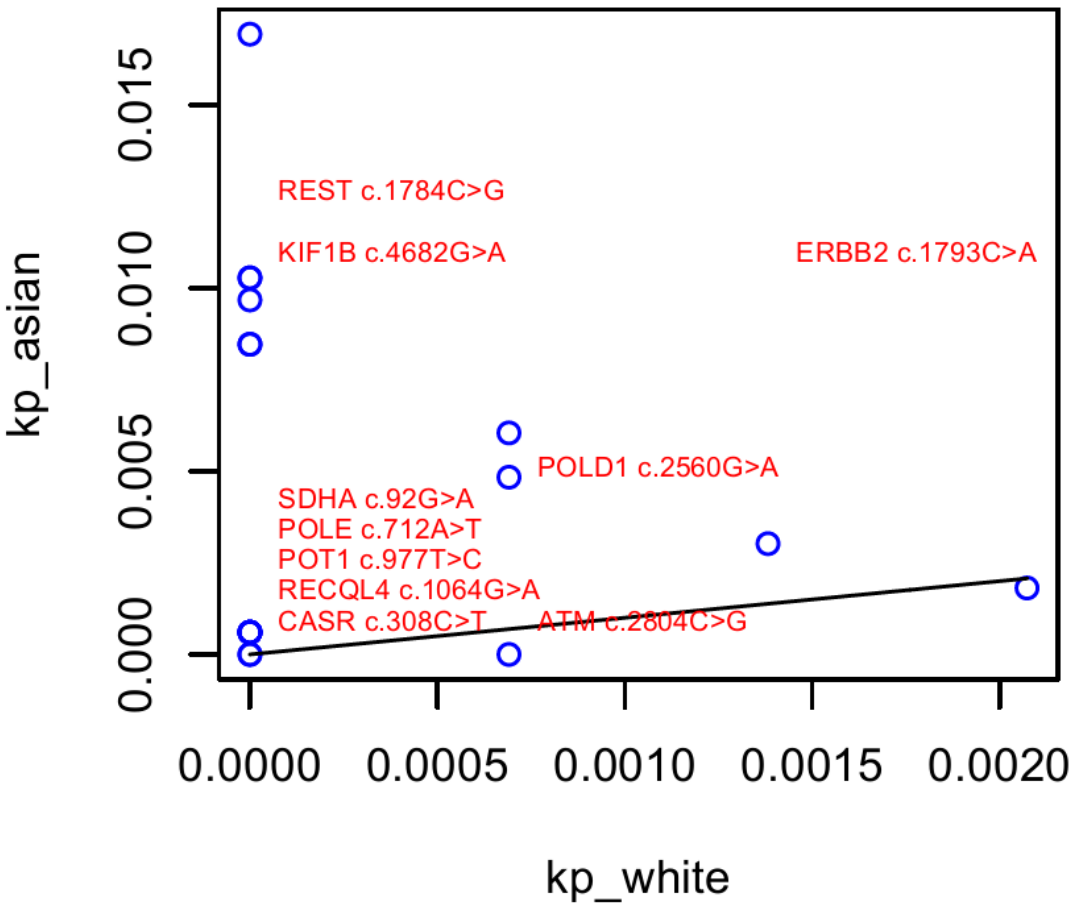
Progressive allele frequency enrichment

VUS – Cancer vs. Ancestry associations

Cancer (Ancestry)



Ancestry (Cancer)



CESR_MM Updates

✓Gene names change

✓Variant nomenclature changes

✓Variant classification changes

	Marker	Variant	Variant Classification	Count
1	ABRAXAS1	c.941A>G	UNCERTAINSIG	129
12	ABRAXAS1	c.941A>G~p.Asn314Ser	UNCERTAINSIG	31
18	FAM175A	c.941A>G	UNCERTAINSIG	21
13	ACADVL	c.1226C>T	PATHOGENIC	29
65	ACADVL	c.1226C>T~p.Thr409Met	PATHOGENIC	7
438	ACADVL	c.1226C>T	UNCERTAINSIG	2
1270	ACADVL	c.1226C>T	PATHLIKELY	1

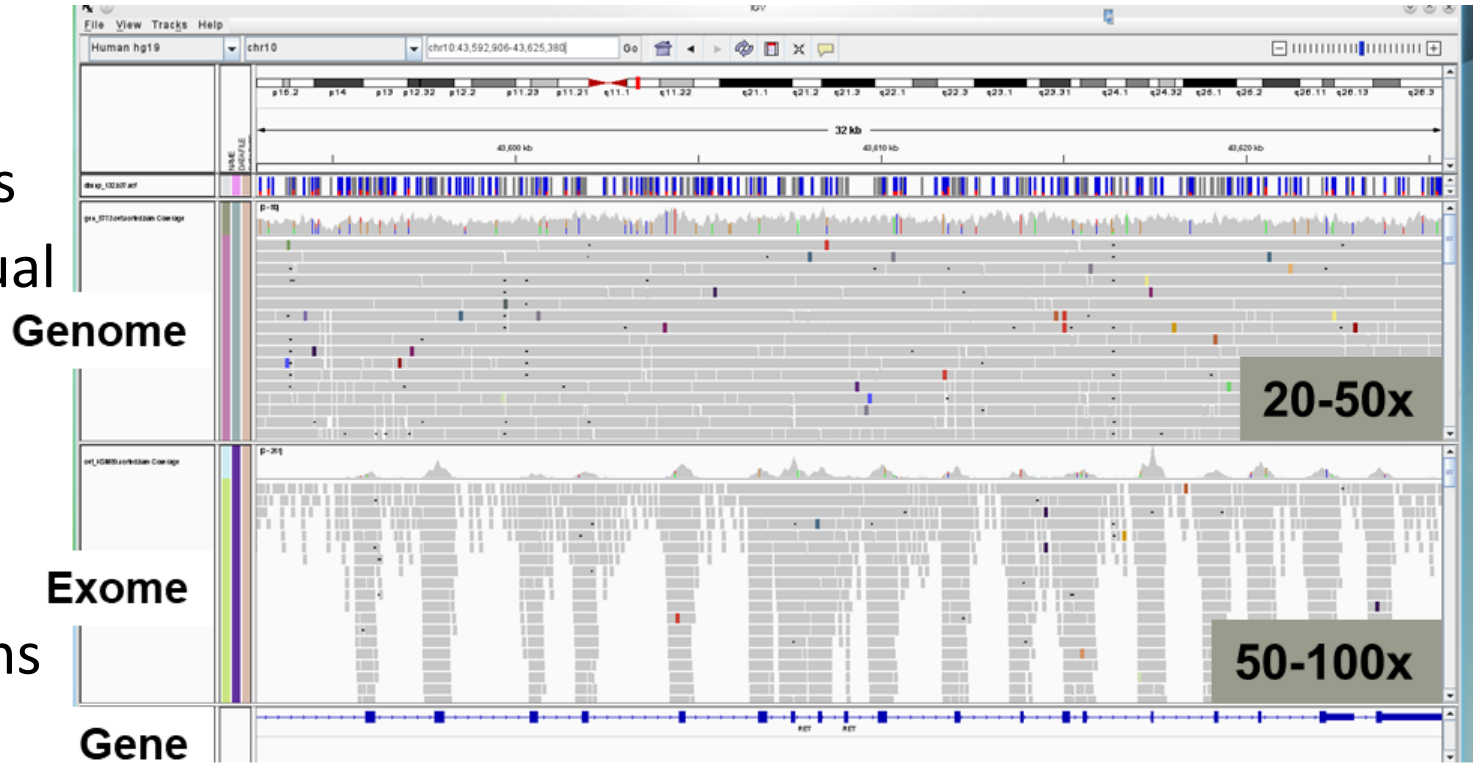
- Gene transcript:variant → genome position (**Common Data Model**)

Overview

- Describe genomics in healthcare and actionable diseases
- Genetic testing in the Virtual Data Warehouse (VDW)
- **Integrating clinical genetic testing and research genomics**
- Improving access to genetic health services

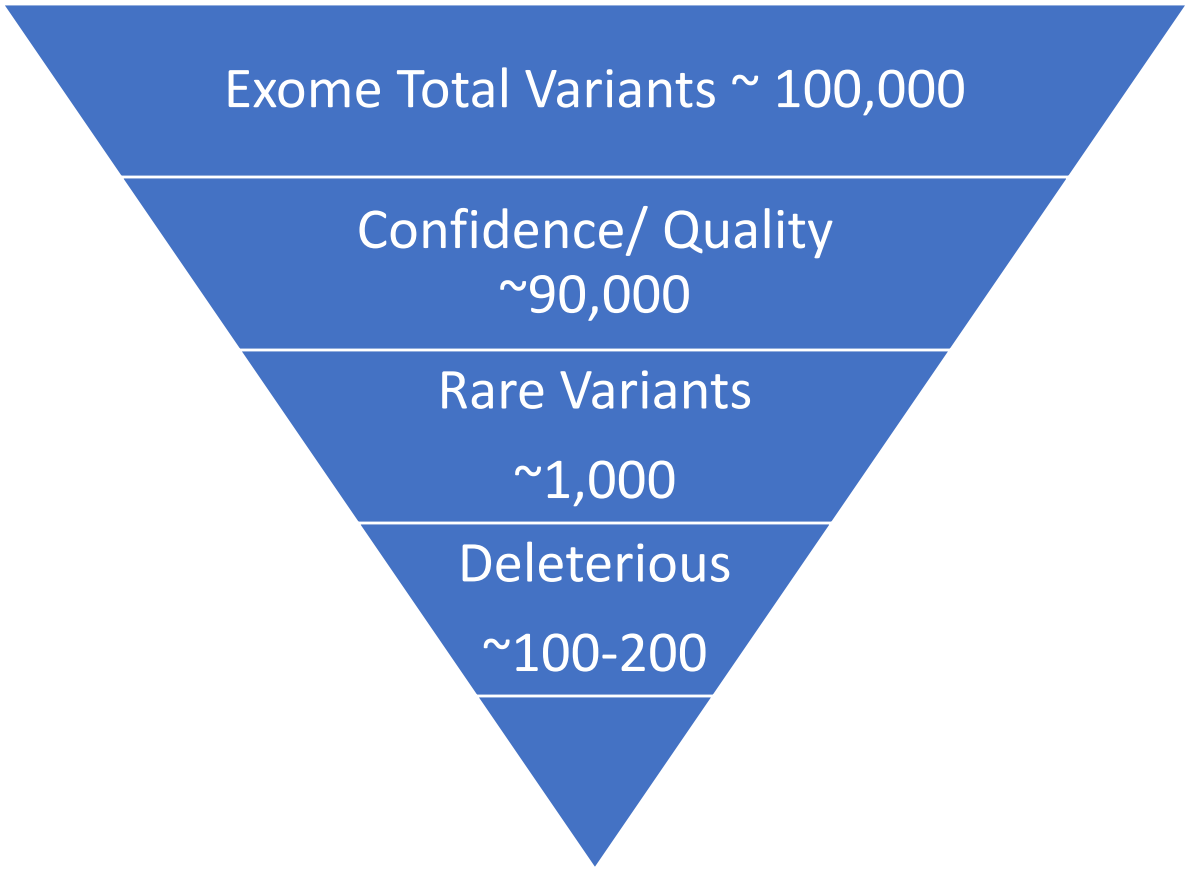
Exome vs Genome

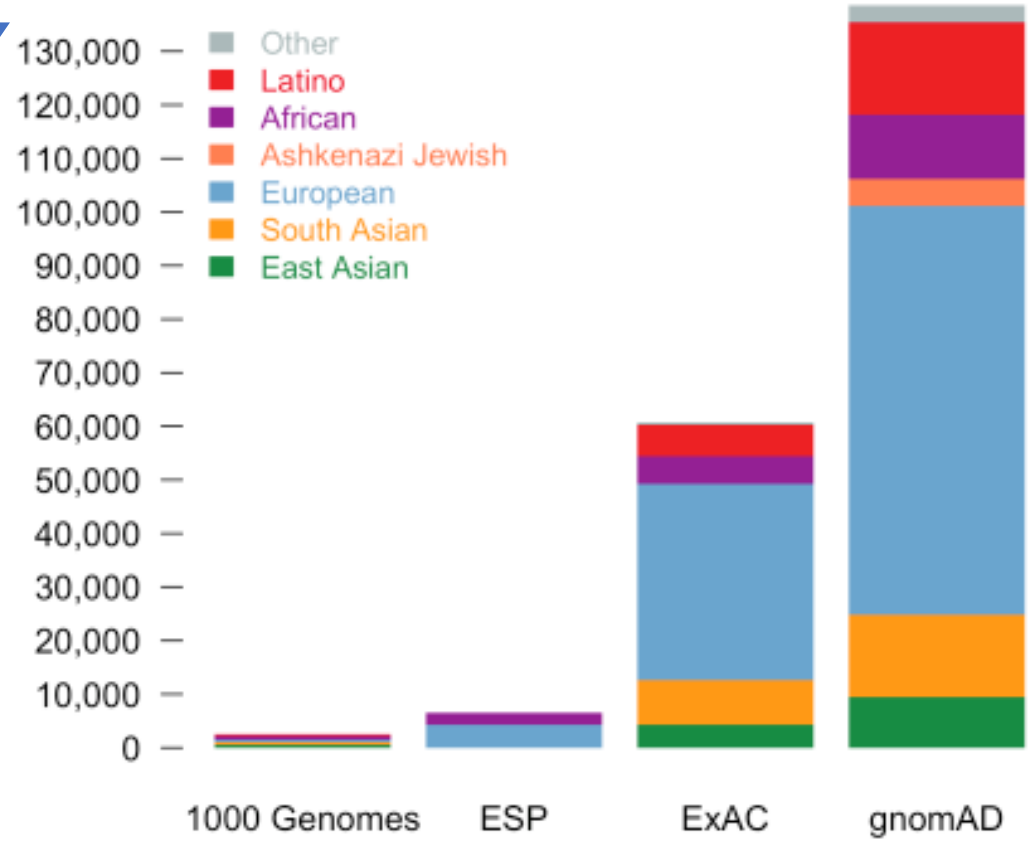
- **Exome sequencing**
  - Typically >99% exon coverage across genome (~2%)
    - Exons, intron/exon boundaries
  - Typical read depth 50-100X+
    - Lower than custom gene panels
  - Detects ~100k variants per individual
  - ~$150-250 reagent cost (U.S.)



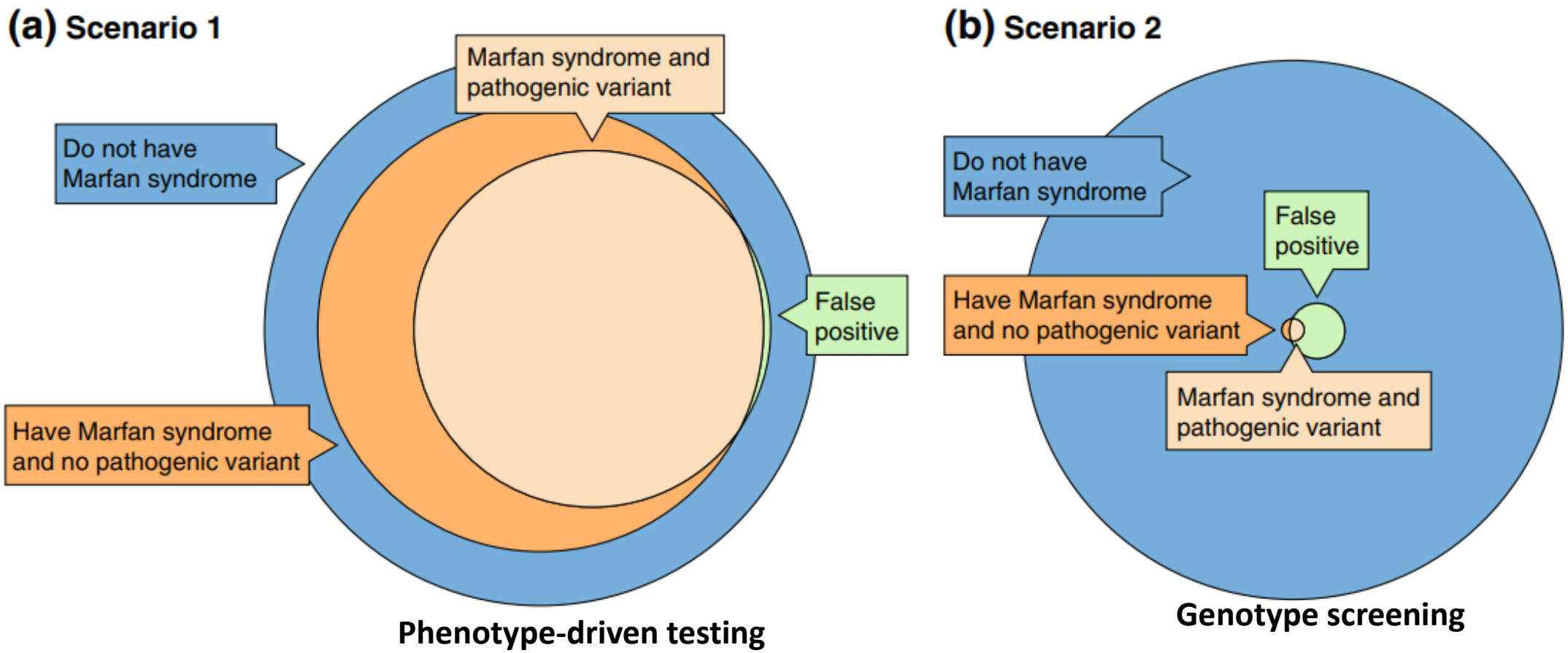
- **Genome sequencing**
  - Genes, inter- and intra-genic regions
  - No enrichment step
  - Low depth for high breadth of coverage (~20-50X)
  - Detects ~4-5M variants per individual
  - ~$200-300 reagent cost at massive scale (2023)

Variant calling and prioritization





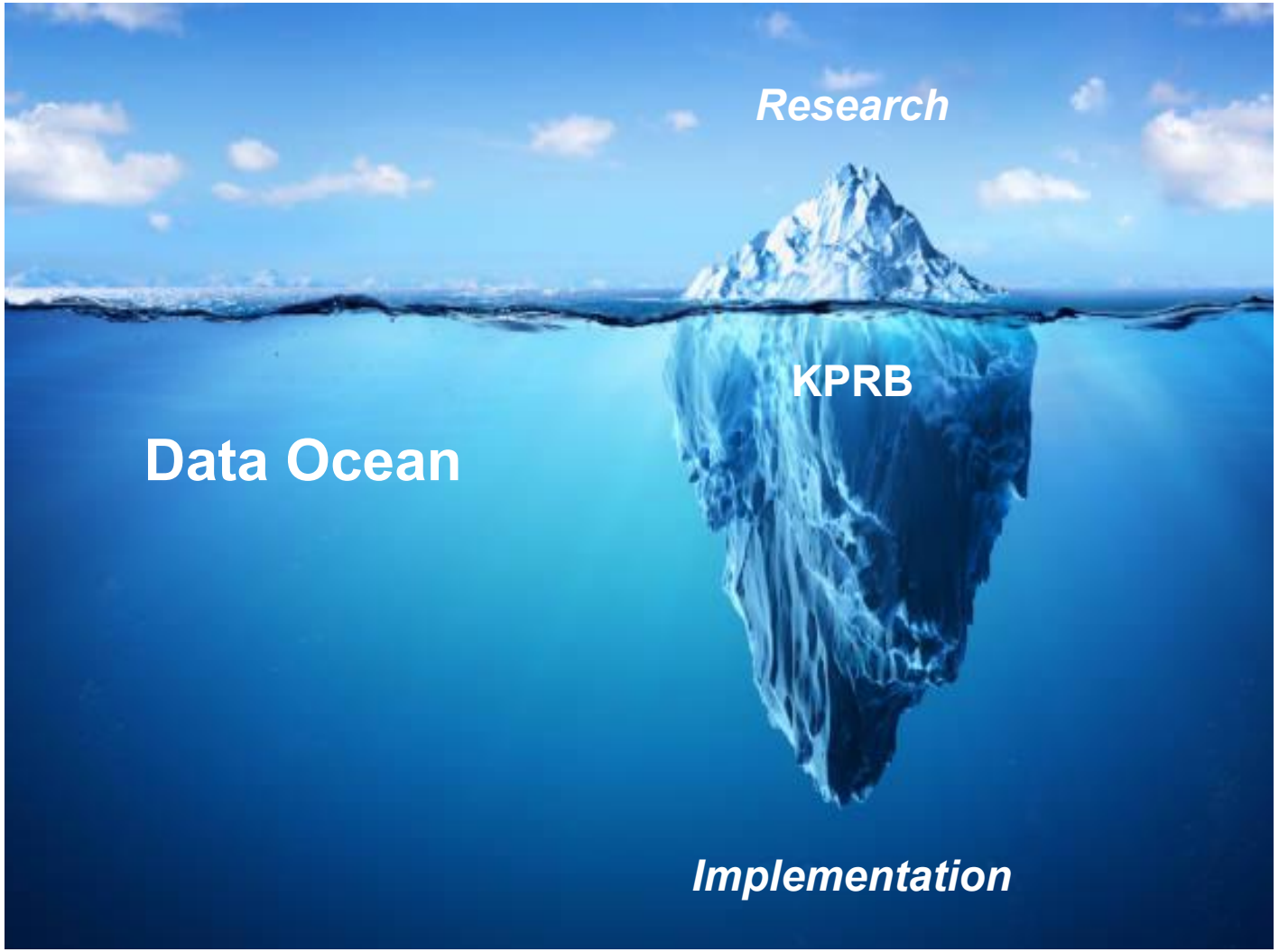
Diagnostic Genetics vs Population Screening



Biesecker, LG, *Genome Medicine* (2019)

KPRB as a hub for both research and healthcare delivery

- Enhanced research data
  - PRS catalog
  - Curated genomic data
- Mission-aligned projects
- Implementation testing
  - Precision Medicine
  - Genetics and Genomics



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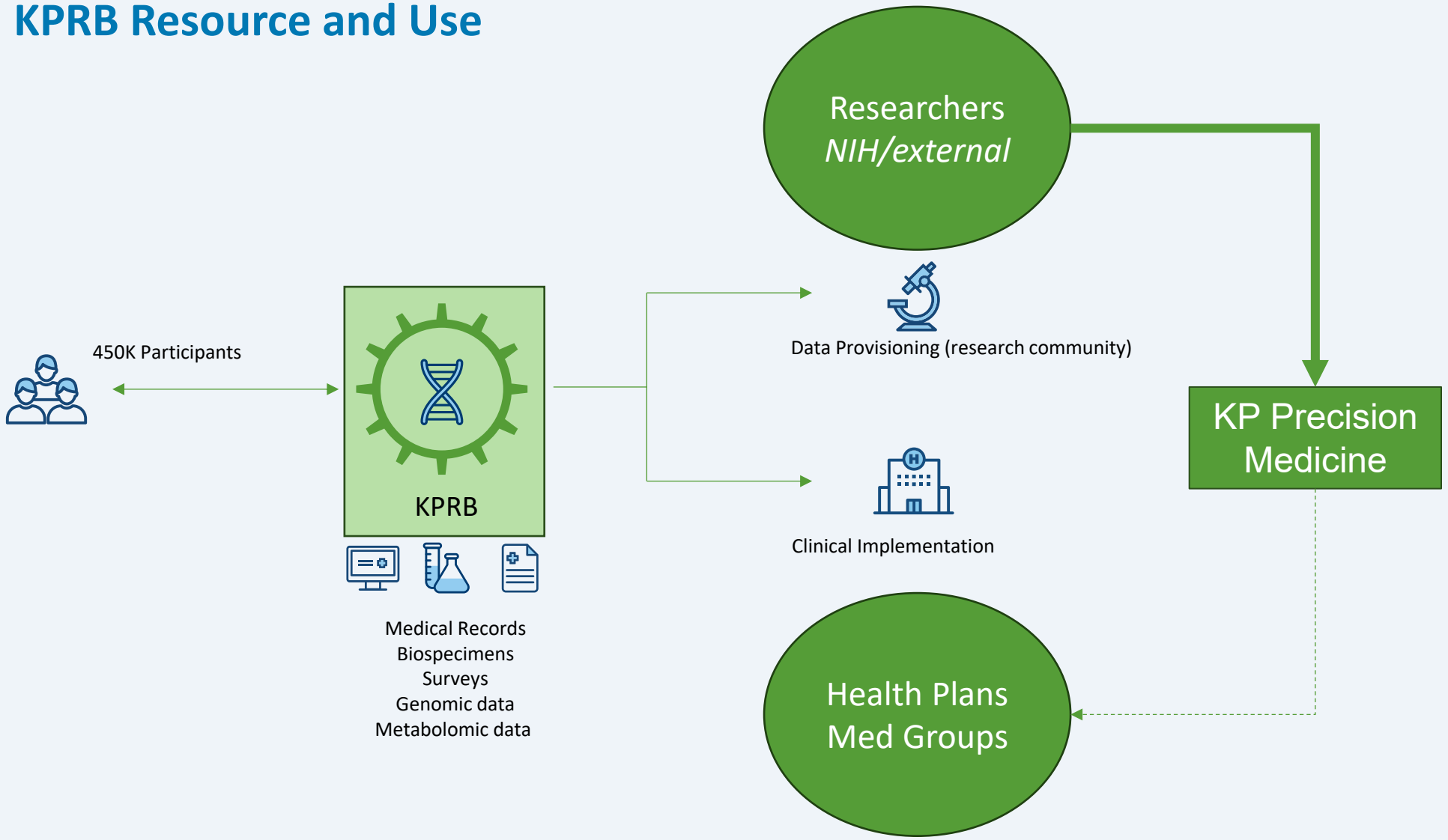
KPRB Resource and Use



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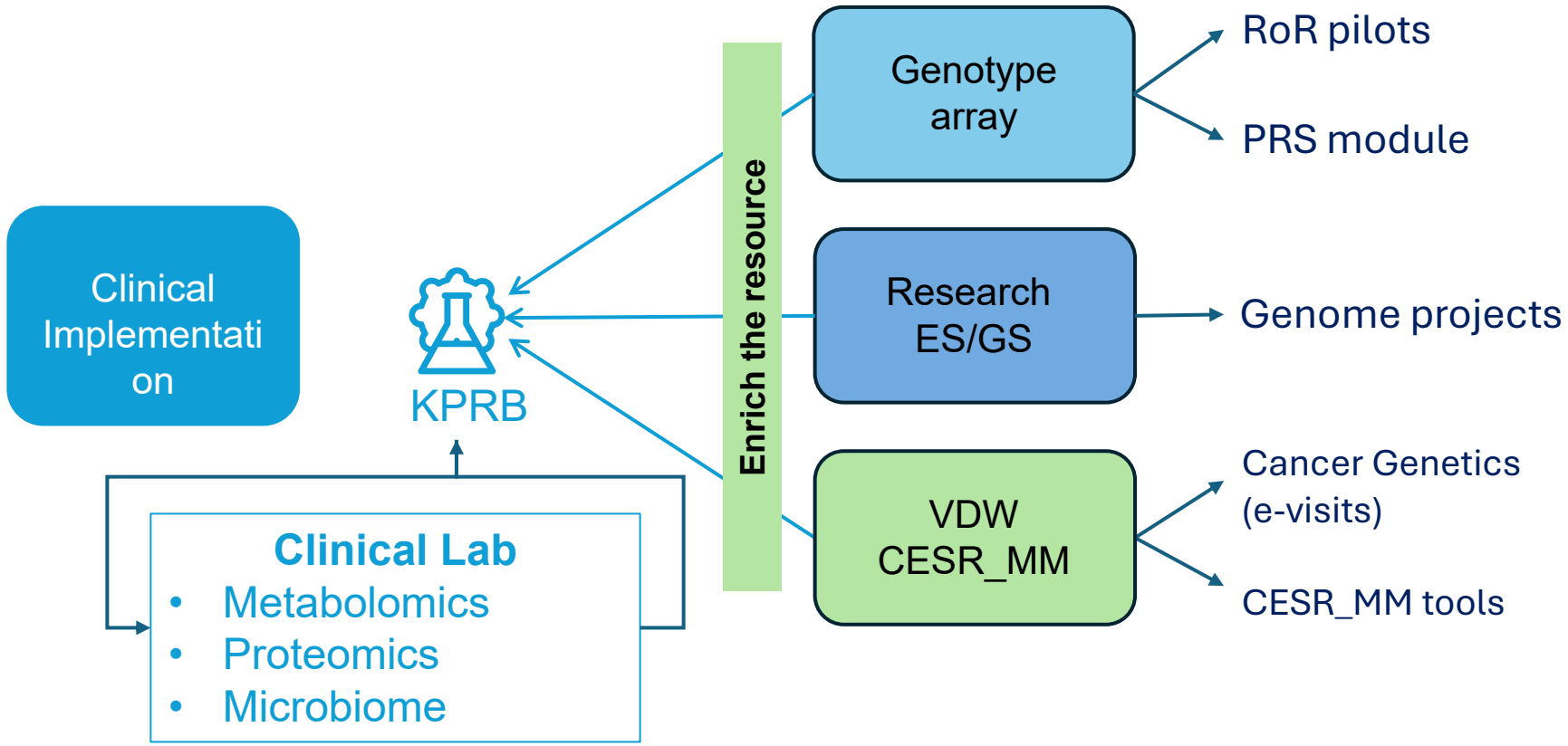
Clinical Implementation – a “living” genetic database

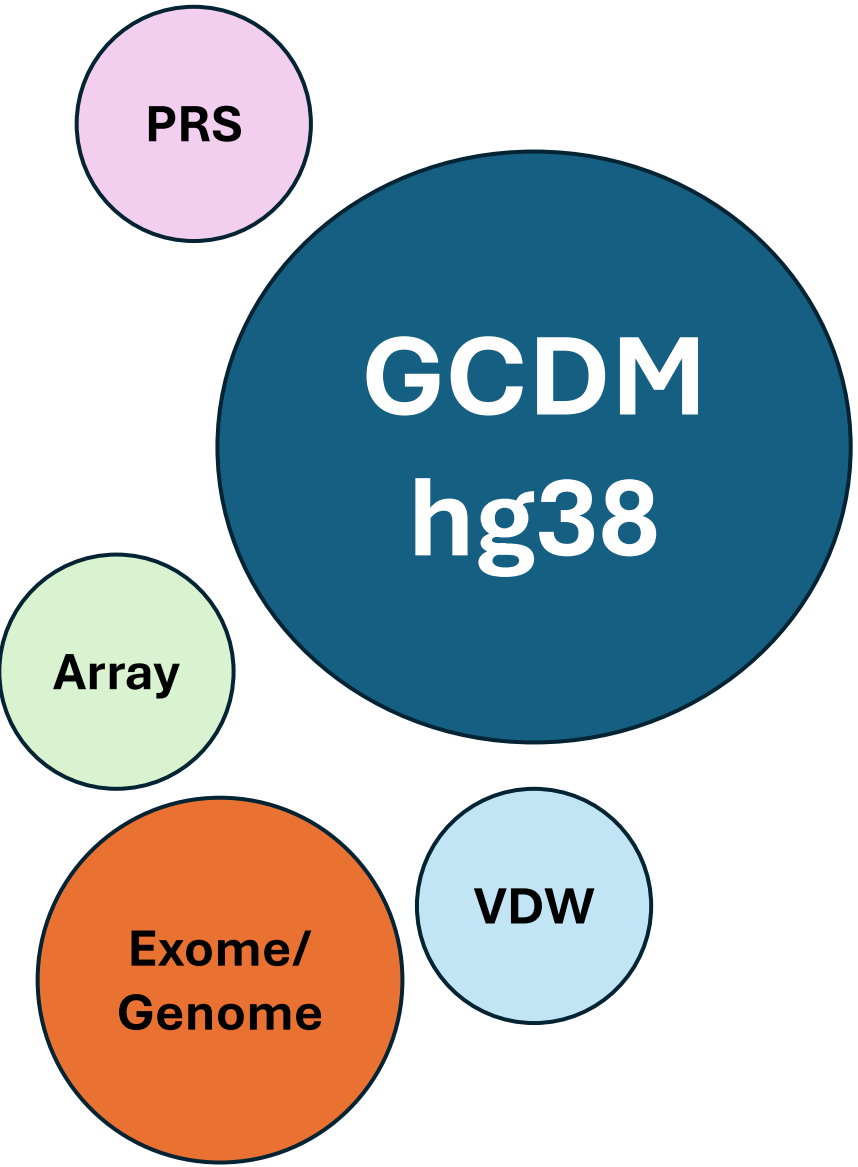
Variant Warehouse

Participant-level genome models

- Genotype array and imputations
- VDW data
- Exome, Genome: actionable findings
- Genome, Array: PRS, PGx

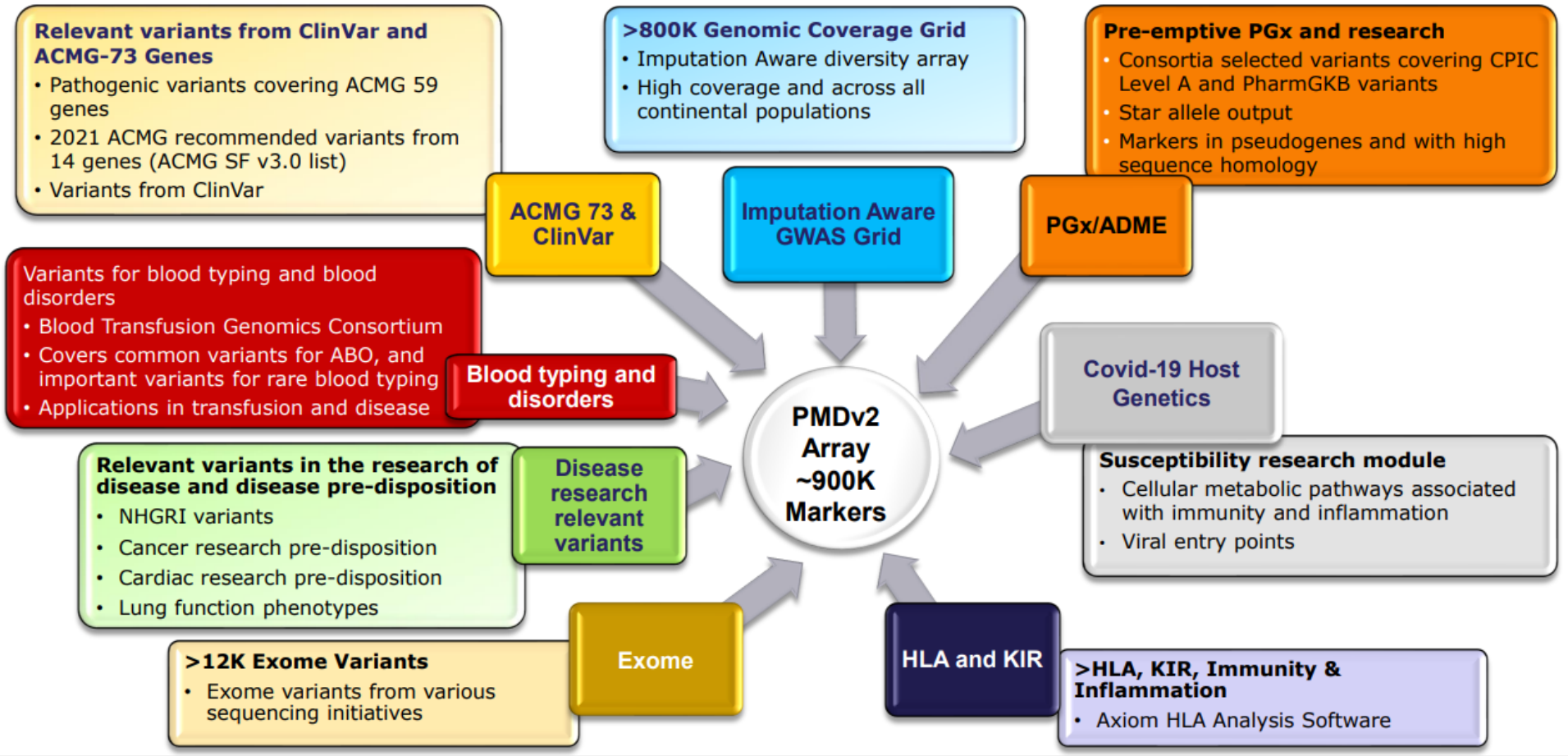


Why a Genomics Common Data Model?



- Ease of search for researchers and users
- Internal validation of genetics data
- Pre-clinical confirmation for return of results
- Enabling collaboration with other biobanks
  - *All of Us*
  - *UK Biobank*
  - *Geisinger/Regeneron*
- *Clinical-grade federated KP variant database*

Axiom™ PMDv2 Array Modules



ThermoFisher SCIENTIFIC

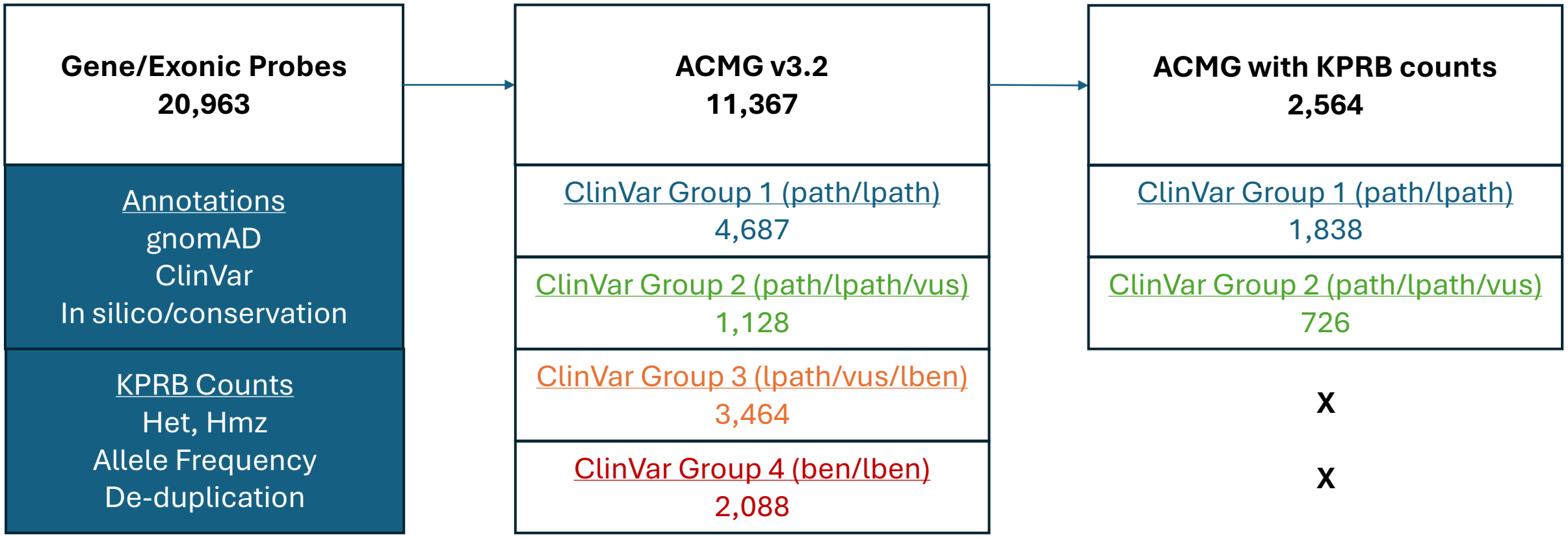
GWAS >800,000

Genes ~24,000

- **ACMG ?**
- **ClinVar ?**
- Exome >12k

Variant clinical relevance?

False +, - rate?



Many thanks to Justin Chan, Anand Sethuraman, and Dilrini Ranatunga (KPRB), Bin Guan (NEI)

ROR Pilot Summary

- Collaboration with KP Southern California genetics and genetic counseling (Monica Alvarado)

- 15 participants at SCAL, 1 at KPHI with pathogenic variants in HBOC and Lynch syndrome genes by array data
  - 7 with prior genetic testing – 100% match to array+Sanger
  - 5 KPRB contacted, SCAL tested – 100% match, cascade testing
  - 3 no longer part of KPRB

- Planning patient experience survey and pilot expansion

Overview

- Describe genomics in healthcare and actionable diseases
- Genetic testing in the Virtual Data Warehouse (VDW)
- Integrating clinical genetic testing and research genomics
- **Improving access to genetic health services**

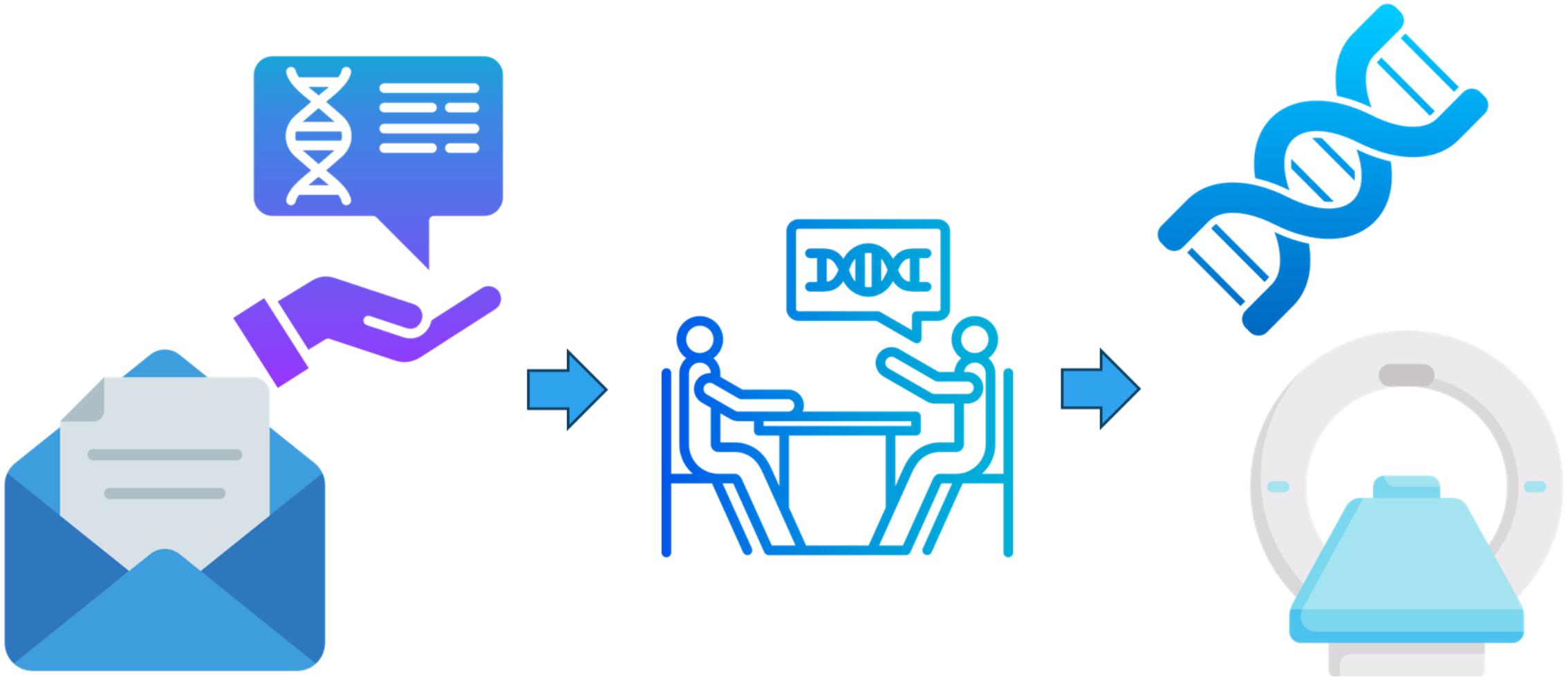
Genetic Counseling

- Board-certified (ABGC), often licensed and credentialed clinical providers
- Assess person's risk for genetic conditions and aid in test selection
- Explain testing benefits, risks, and expectations (pre-test)
- Explain results and follow-up testing in family members (post-test)
- Practice independently or with physicians (genetics, oncology, etc)
- **Integral part of multidisciplinary care team!**

E-Visit Pilot

- Access to cancer genetic screening, counseling, and testing is limited
- E-visit = 3-minute online survey (kp.org) coveringcancer family history and triggering GC-visit (
- Goal – population screening for enhanced surveillance and testing
- **Screen Eligibility -** female at birth, and age 30–45. Exclusion criteria were a current or prior cancer diagnosis, or a genetic counseling appointment for cancer within the past three years.
- **Pilot Design - i**nvitations were first sent to 45-year-olds, then expanded to younger age groups based on response rates. New members and those with interval birthdays were included in subsequent rounds.
- **Screen-Positive Actions**
- Members with screen-positive results were scheduled for a telephone consultation with a genetic counselor for pre-test genetic counseling and independent assessment for genetic testing criteria and cancer risk.
- Pre-test genetic counseling was performed with NCCN guidelines utilized for HBOPP criteria for genetic testing. Breast cancer risk assessments used the Tyrer-Cuzick Model (version 8.0b).
- Those with a lifetime breast cancer risk over 20% were enrolled in the high-risk screening registry, initiating alternating mammography and breast MRI every six months at the appropriate age.
- A “safety net” ensured recontact for members who screened positive but did not schedule.

E-Visit Workflow



Sent e-visit:
34,201

Started e-visit:
25,002

Completed survey:
4,508

Screened positive:
1,577

Agreed to GC visit:
1,262

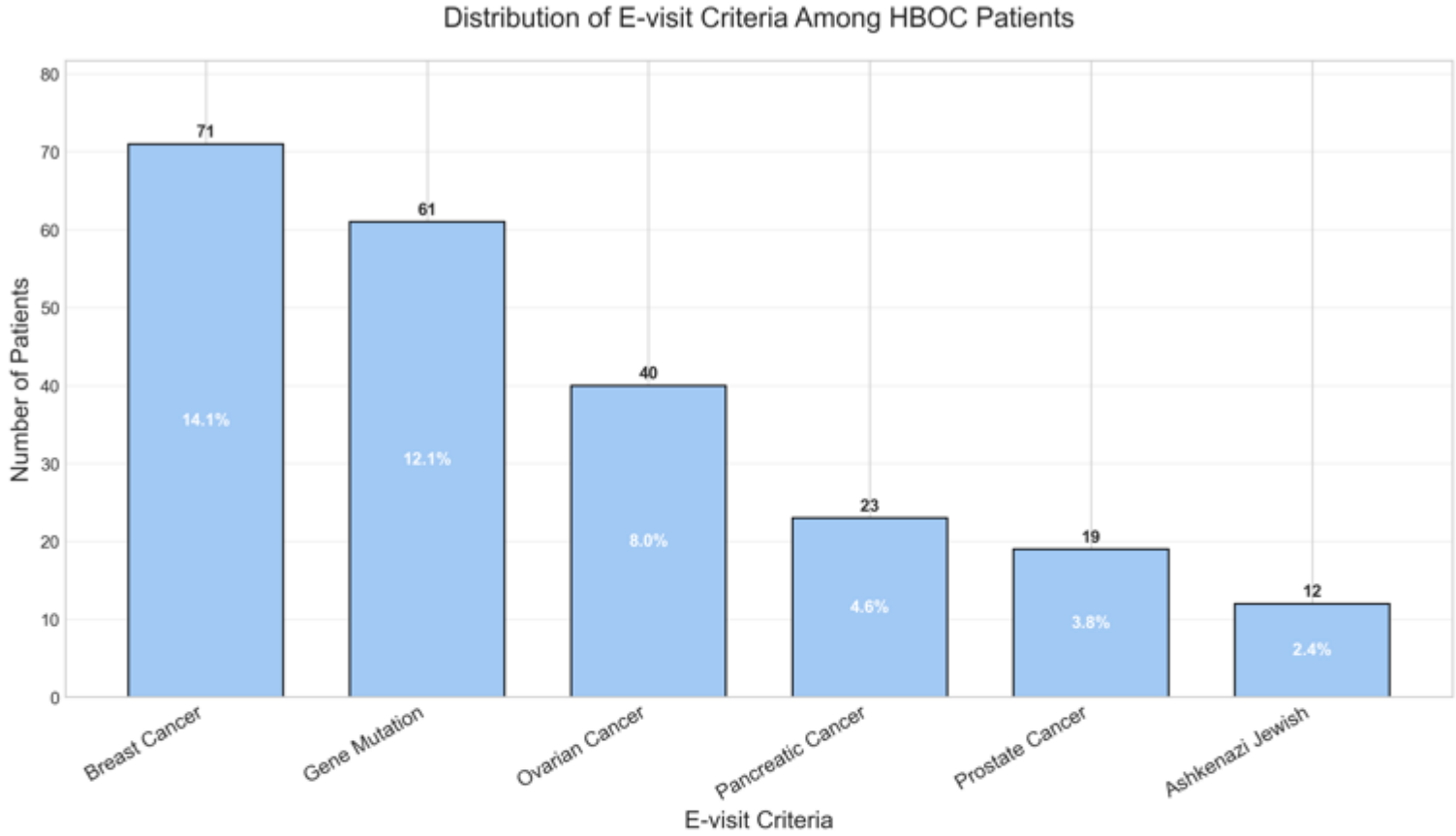
Scheduled GC visit:
856

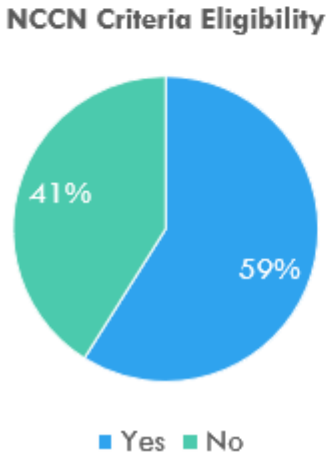
Completed GC visit:
720

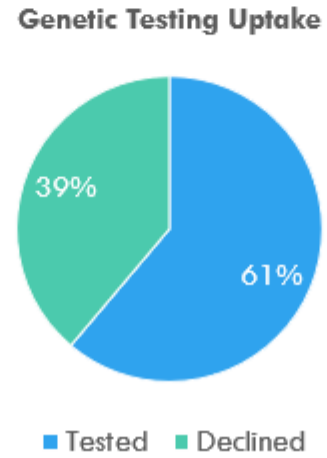
Met NCCN Criteria for Genetic Testing:
422

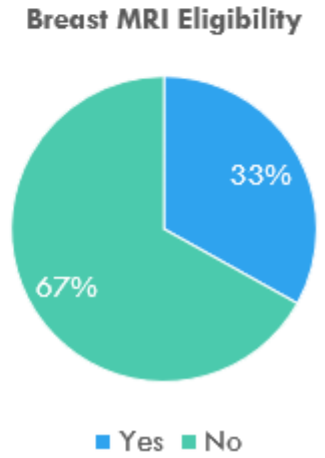
Agreed to Genetic Testing:
208

High Risk Screening MRI Eligible:
237









Key Observations

- **E-visit survey had a high screen-positive rate: ~33%**
  - NCCN eligibility accuracy ~59% (=41% false positives)
  - Corrected by direct genetic counseling visits
- **Breast MRI eligibility ~33%**
  - Genetic counseling identified those needing high risk MRI screening even if not eligible for genetic testing
- **Genetic testing yield was similar though slightly lower than direct referrals (5.6%)**
  - Expected with population screening
  - 39% of eligible patients declined when provided genetic counseling
- **Summary – genetic counseling corrected screening inaccuracies, identified those requiring enhanced surveillance regardless of genetic testing, and provided patients with informed consent.**

Conclusions

- Utilization and utility of clinical genetic testing is increasing
- Clinical genetic testing generates discrete data types
- CGDM using HGVS standards is required for interoperability
- Variant re-classification through laboratories may resolve uncertainty

Population Health

Acknowledgements

Kaiser Permanente Research Bank

- Devin Absher (Vice President)
- Sarah Rowell (Senior Director)
- Anand Sethuraman (Data Resource Ecosystem Lead)
- Dil Ranatunga (Data Provision and Analytics Lead)
- Alex Lituev (Biorepository Lead)

CESR Molecular Marker Workgroup

- **Melanie Francisco, KPNW**

CESR
Kaiser Permanente Center for Effectiveness & Safety Research

Center for Integrated Healthcare Research

CIHR & Hawaii Permanente Medical Group

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- Kathy Higuchi (Director, Research Administration)
- Valentyna Pishchalenko (Supervising Analyst)
- Tim Frankland (Analyst)
- Priscila Adolfson (Analyst)

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