

**Enhanced
CARE for RARE
Genetic
Diseases in
Canada**



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Head and Associate Professor,
Department of Medical Genetics
University of Calgary
Canada



21 Sites

80 Physicians

50 Scientists

Shared Pipeline and Resources

>1300 Diseases Proposed

- Caused by 1 gene?
- All clinical testing complete?
- Patient lives in Canada?

>1000 Diseases Selected for Study



**CARE
forRARE**

Shared Pipeline and Resources



THE HUMAN PHENOTYPE ONTOLOGY PhenomeCentral collects phenotype data using the Human Phenotype Ontology (HPO), a	THE EXOMISER The Exomiser software package	THE MONARCH INITIATIVE The Monarch Initiative builds and maintains a curated knowledge base that links genomic phenotypes	PHENOTIPS™ PhenomeCentral was built on top of Phenotips, an open source software for collecting and analyzing
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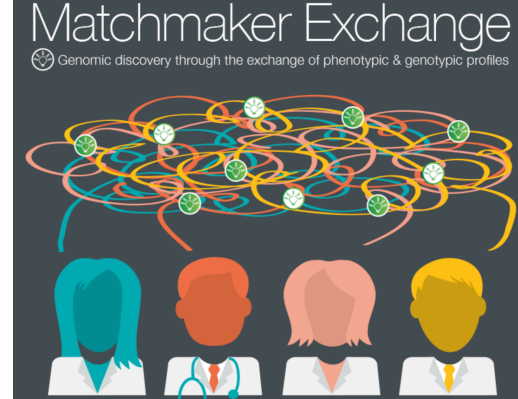


Analysis Teams



Matchmaker exchange

Matchmaker Exchange | Connected Nodes



Exome sequencing



MD_combined_variants - Microsoft Excel

File Home Insert Page Layout Formulas Data Review View

Calibri 11 A A

General

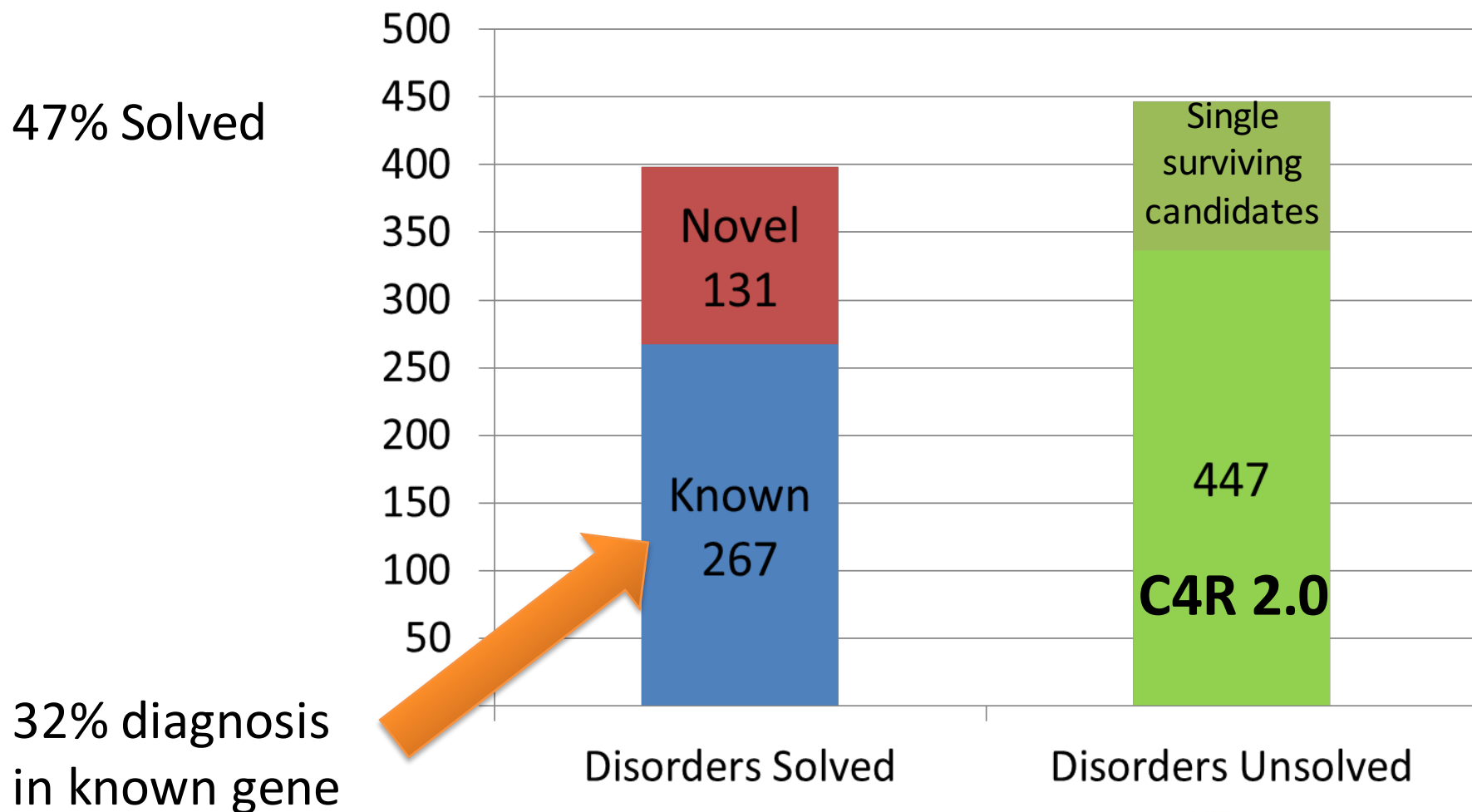
Normal Bad Good Neutral Calculation

Check Cell Explanatory... Hyperlink Input Linked Cell

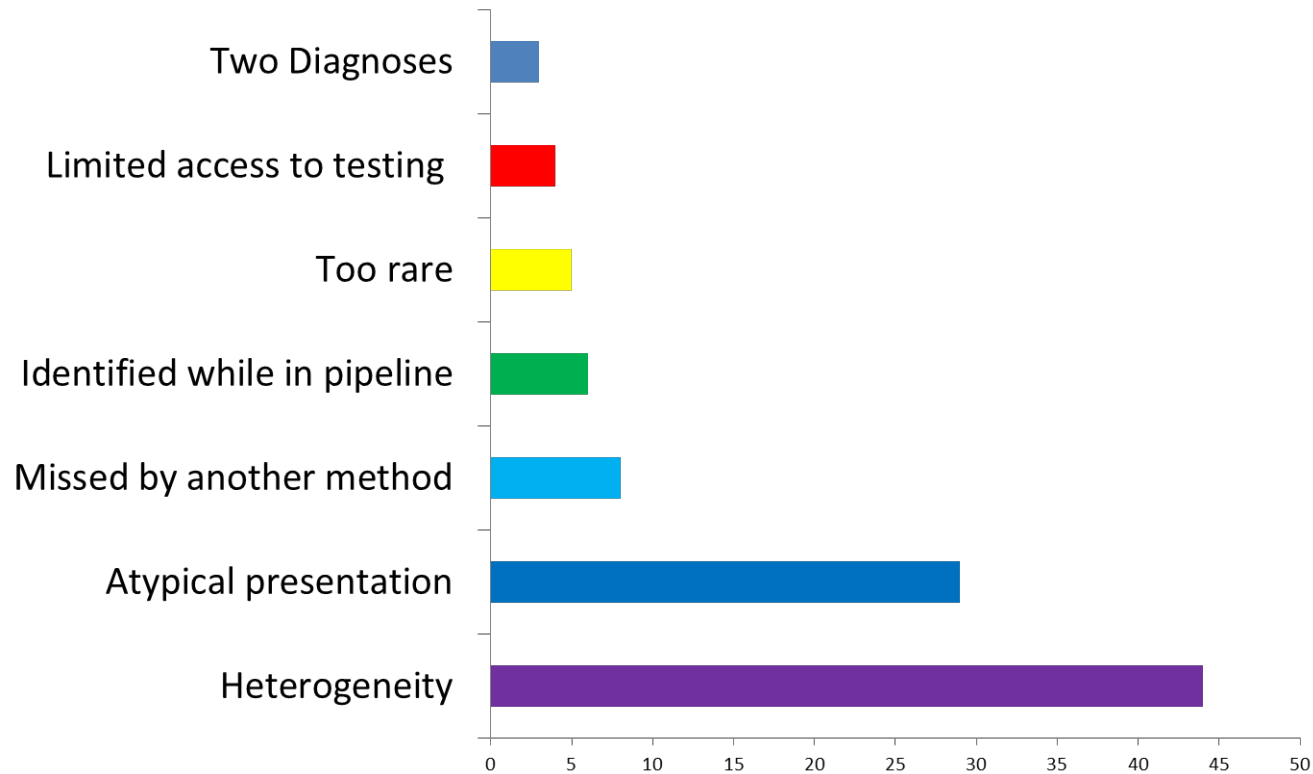
AF55 336

Position	UCSC Browser	Variation	Ref Alt	Mutation considered rare/significant	M1-1 homozygosity	M1-5 homozygosity	M11-1 homozygosity	M13-1 homozygosity	M9-1 homozygosity	M23-1 homozygosity	#Non-affected samples with this mutation	#Affected samples with this mutation	#Affected samples with this gene mutated	#Affected homozygotes in this gene	#Affected multiple hets for gene	#Affected hom DR multiple het	MapQ-Mapping quality	Gene	Gene mutation frequency in 277 control samples (gene rank, #rare mutations, #truncating mutations)	# prev samples	Prev seen samples	dbSNP rsID	MAF from 1000 Genomes	MA F from EV	EVs Genotype Counts (hom alt, het, hom)	PhastCons
chr10:5257377	UCSC link	nonsynonymous SNV C	T	0	-	het	-	-	-	-	3	1	0	0	0	0	60	ATCF	3641.7:2	4	KB_JB_07_2082	rs1427405	0.004	0.5	0.58:53:1	748
chr12:8975873	UCSC link	nonsynonymous SNV C	G	0	-	het	-	-	-	-	3	1	0	0	0	0	60	A2ML1	750.15:2	4	AD_MTA_1932.F	rs7949329	0.001	0.3	1.23:48:8	285
chr3:5154535	UCSC link	stoploss SNV T	C	0	-	-	-	-	-	het	3	1	0	0	0	0	60	AADAC	12623.2:0	4	KB_MFDM_2005	rs6173368	0.002	0.4	0.45:51:6	359
chr4:5720494	UCSC link	nonsynonymous SNV A	G	1	het	-	-	-	-	-	1	1	0	0	0	60	AASDH	6071.5:1	2	AD_P28_1994.M	rs11857168	0.001	0.1	0.14:53:5	436	
chr17:7910496	UCSC link	nonsynonymous SNV C	T	1	het	-	-	-	-	-	0	1	0	0	0	60	AAIK	57117.1	1	M1-5	-	0.001	0.1	0.9:50:10	295	
chr3:10765147	UCSC link	exonic splicing C	T	1	het	-	-	-	-	-	1	1	0	0	0	60	ABCA1	269.22:3	1	M1-1	-	0	-	549		
chr2:21591723	UCSC link	nonsynonymous SNV G	A	1	-	-	het	-	-	-	0	1	0	0	0	60	ABCA1	438.19:0	1	M11-1	-	0	0.1	0.10:53:68	385	
chr2:21588274	UCSC link	nonsynonymous SNV T	C	0	-	-	-	het	-	-	3	1	0	0	0	60	ABCA12	438.19:0	4	NJ_ATTRT38_tumor_KB_208	rs1139035	0.003	0.8	0.83:52:96	437	
chr7:48319405	UCSC link	nonsynonymous SNV A	C	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17192311	0.012	1.5	0.143:45:93	378	
chr7:48315724	UCSC link	nonsynonymous SNV C	T	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17192311	0.011	1.5	0.140:46:16	378	
chr7:48314925	UCSC link	nonsynonymous SNV T	A	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17132197	0.013	1.5	0.140:45:96	378	
chr7:48312493	UCSC link	nonsynonymous SNV G	A	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs11670538	0.011	1.5	0.142:46:10	378	
chr7:48316614	UCSC link	nonsynonymous SNV T	G	0	-	-	-	-	-	het	5	1	0	0	0	60	ABCA13	32.47:4	6	WDF_17461.NJ-GEM-1111.NJ	rs11564116	0.011	1.5	0.142:45:76	378	
chr7:48318400	UCSC link	nonsynonymous SNV T	G	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17132206	0.011	1.5	0.144:46:49	378	
chr7:48313252	UCSC link	nonsynonymous SNV A	G	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs7594833	0.011	1.5	0.142:45:76	378	
chr7:48352693	UCSC link	nonsynonymous SNV A	G	0	het	het	-	-	-	-	6	2	1	0	0	60	ABCA13	32.47:4	8	RK_210_61.DT_2	rs11260604	0.022	2.3	5.208:46:26	378	
chr7:48317836	UCSC link	nonsynonymous SNV G	A	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs111564116	0.011	1.5	0.139:45:56	378	
chr7:48315363	UCSC link	nonsynonymous SNV A	G	0	-	-	-	het	-	-	7	1	0	0	0	60	ABCA13	32.47:4	8	ES_316-Falschle	rs17661366	0.039	2.7	7.244:45:20	378	
chr7:48313563	UCSC link	nonsynonymous SNV A	G	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17132195	0.011	1.5	0.142:45:24	378	
chr7:48450185	UCSC link	nonsynonymous SNV C	G	0	-	-	het	-	-	-	4	1	0	0	0	60	ABCA13	32.47:4	5	NJ_ATTRT_AK388	rs7714747	0.006	1	2.95:50:68	378	
chr7:48311802	UCSC link	nonsynonymous SNV G	A	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs11623939	0.012	1.5	0.138:46:15	378	
chr7:48318096	UCSC link	nonsynonymous SNV A	G	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17132206	0.011	1.5	0.143:46:33	378	
chr7:48314151	UCSC link	nonsynonymous SNV C	G	1	het	-	-	-	-	-	0	1	0	0	0	60	ABCA13	32.47:4	1	M1-1	-	0.003	0.7	0.64:47:52	378	
chr7:48315896	UCSC link	nonsynonymous SNV T	C	0	het	het	-	-	-	-	5	2	1	0	0	60	ABCA13	32.47:4	7	RK_210_61.DT_2	rs17132198	0.011	1.4	0.131:45:91	378	
chr1:94480146	UCSC link	nonsynonymous SNV T	C	1	-	-	het	-	-	-	0	1	2	0	0	59	ABCA4	1633.11:1	1	M11-1	rs1675302	0	-	-	682	
chr1:94568675	UCSC link	nonsynonymous SNV T	C	1	-	-	-	het	-	-	1	1	2	0	0	60	ABCA4	1633.11:1	2	NJ_ATTRT38_tumor_KB_208	rs11246700	0.003	0.1	0.11:53:68	455	
chr1:22966595	UCSC link	nonsynonymous SNV C	T	0	het	-	-	het	-	-	4	2	0	0	0	60	ABCB10	8345.4:0	6	TLY_MD_FAM66	rs3569879	0.006	1	1.107:52:71	346	
chr2:16982853	UCSC link	nonsynonymous SNV C	T	1	-	-	-	-	het	-	0	1	0	0	0	60	ABCB11	1808.10:6	1	M3-1	-	5E-04	0	0.150:20	632	
chr2:22008141	UCSC link	nonsynonymous SNV G	A	0	-	het	-	-	-	-	4	1	0	0	0	60	ABCB6	4537.6:3	5	NJ_ATTRT13_tumor	rs5746791	0.006	1.1	0.118:52:57	429	
chr7:15073096	UCSC link	nonsynonymous SNV C	G	1	-	-	-	-	het	-	0	1	0	0	0	60	ABCB8	6615.5:0	1	M3-1	rs11779310	0.003	0.8	0.81:52:98	477	
chr16:1614207	UCSC link	nonsynonymous SNV G	T	0	het	-	-	-	-	-	3	1	0	0	0	60	ABCC1	501.18:0	4	DT_14_NJ-GEM-F	rs6078212	0.004	0.9	1.92:50:92	494	
chr16:16218681	UCSC link	nonsynonymous SNV G	A	1	-	-	-	het	-	-	0	1	0	0	0	60	ABCC1	501.18:0	1	M3-1	-	0	-	371		
chr6:43411932	UCSC link	nonsynonymous SNV A	G	0	-	-	het	-	-	-	2	1	0	0	0	60	ABCC10	806.15:0	3	PT_N5668.MCC_VF3.M11-1	rs11246700	5E-04	0.3	1.23:53:49	470	
chr16:4825015	UCSC link	nonsynonymous SNV C	A	1	-	het	-	-	-	-	0	1	0	0	0	60	ABCC11	663.16:1	1	M1-5	-	5E-04	0	0.2:53:77	470	
chr13:3570538	UCSC link	nonsynonymous SNV G	A	0	-	het	-	-	-	-	4	1	0	0	0	60	ABCC4	7693.4:1	5	KB_208_4404.WDF_16344.A	rs16344	0.003	0.6	0.62:53:17	597	
chr16:1627634	UCSC link	nonsynonymous SNV C	T	0	-	-	-	-	-	het	5	1	0	0	0	59	ABCC6	1495.11:5	6	NJ_ATTRT_PS006	rs5807378	0.012	1.7	2.178:51:99	597	
chr11:1743003	UCSC link	nonsynonymous SNV T	C	1	-	-	het	-	-	-	0	1	0	0	0	60	ABCC8	867.14:3	1	M11-1	-	0	-	545		
chr14:7475673	UCSC link	nonsynonymous SNV G	A	1	-	-	-	het	-	-	1	1	1	0	0	59	ABCD4	1254.12:3	2	NDCML_19374.M1	rs4556833	0.001	0.1	0.14:53:65	502	
chr11:11902731	UCSC link	nonsynonymous SNV G	A	1	-	het	-	-	-	-	0	1	0	0	0	60	ABCG4	12626.2:0	1	M1-5	-	0	-	545		
chr17:4729755	UCSC link	nonsynonymous SNV G	A	1	-	-	-	het	-	-	0	1	0	0	0	60	AB13	3946.7:2	1	M15-1	-	0	-	545		
chr10:11633116	UCSC link	nonsynonymous SNV C	T	1	-	het	-	-	-	-	0	1	0	0	0	60	ABLIM1	6616.5:0	1	M1-5	-	0	-	493		
chr3:1361363	UCSC link	nonsynonymous SNV C	T	1	-	het	-	-	-	-	0	1	0	0	0	59	ABO	6072.5:1	1	M1-5	rs1676730	0	0.1	0.11:49:67	493	
chr3:1213677	UCSC link	nonsynonymous SNV C	T	0	het	-	-	-	-	-	6	1	0	0	0	60	ABO	6072.5:1	1	ES_316-Falschle	rs1676636	0.022	2.2	1.216:48:12	514	
chr12:1218491	UCSC link	nonsynonymous SNV G	A	1	-	-	-	het	-	-	0	1	0	0	0	60	ABTB1	3041.6:1	1	M3-1	-	0	-	272		
chr17:7127806	UCSC link	nonsynonymous SNV G	A	1	-	-	-	-	het	-	0	1	0	0	0	60	ACAD10	1912.10:2	1	M123-1	-	0	-	272		
chr7:15074785	UCSC link	nonsynonymous SNV C	T	0	het	-	-	-	-	-	7	1	0	0	0	59	ACADVL	4163.7:0	1	M23-1	-	0	-	363		
chr17:6156602	UCSC link	nonsynonymous SNV G	A	1	het	-	-	-	-	-	0	1	2	0	0	60	ACN3	1112.13:1	8	PC_Fib_BKC_NJ	rs11402482	0.006	1	0.104:52:74	363	
chr17:6156183	UCSC link	nonsynonymous SNV A	G	1	-	-	-	het	-	-	1	1	2	0	0	55	ACE	1640.11:1	1	M1-1	-	0	0.2:53:77	470		
chr7:9674719	UCSC link	nonsynonymous SNV T	C	0	-	-	-	-	het	-	4	1	0	0	0	60	ACN9	14579.1:1	1	M23-1	-	0	-	515		
chr5:8064084	UCSC link	nonsynonymous SNV G	A	1	-	-	-	-	-	het	0	1	0	0	0	60	ACOT12	6076.5:1	1	M23-1	-	0	0.3	0.30:53:49	527	
chr4:8418148	UCSC link	nonsynonymous SNV T	G	0	-	-	het	-	-	-	3	1	0	0												

845 disorders out of the pipeline



Why were known genes not identified in the clinic?



Diagnostic utility

**CLINICAL
GENETICS**

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Review

Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care

Sawyer S.L., Hartley T., Dymont D.A., Beaulieu C.L., Schwartzentruber J., Smith A., Bedford H.M., Bernard G., Bernier F.P., Brais B., Bulman D.E., Warman Chardon J., Chitayat D., Deladoëy J., Fernandez B.A., Frosk P., Geraghty M.T., Gerull B., Gibson W., Gow R.M., Graham G.E., Green J.S., Heon E., Horvath G., Innes A.M., Jabado N., Kim R.H., Koenekoop R.K., Khan A., Lehmann O.J., Mendoza-Londono R., Michaud J.L., Nikkel S.M., Penney L.S., Polychronakos C., Richer J., Rouleau G.A., Samuels M.E., Siu V.M., Suchowersky O., Tarnopolsky M.A., Yoon G., Zahir F.R., FORGE Canada Consortium, Care4Rare Canada Consortium, Majewski J., Boycott K.M. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care.

Clin Genet 2015. © 2015 The Authors. *Clinical Genetics* published by John Wiley & Sons A/S. Published by John Wiley & Sons Ltd., 2015

Value and Economic Impact



Education



Analysis and Interpretation



Tools and Guidelines



Cost of Rare Disease



Genetic disease patients cost :

- 20x more than healthy individuals
- 5x more than chronic diseases
(asthma, diabetes)

Chart review of 300 patients with a molecularly-diagnosed genetic disease

Value of a Diagnosis

Discrete Choice Experiment survey with 300
Canadian rare disease families



Families are willing to spend \$5,000 out-of-pocket
for a diagnosis

Most important attributes:

- 1) time to obtain an answer;
- 2) chance of diagnosis;
- 3) cost;

Least Important attributes:

- 1) type of test;
- 2) impact of results.

Education Program



Audience: medical genetics trainees, and interested individuals in current medical genetics practice

Module 1: Technical Aspects

Module 2: Ethical Issues

Module 3: Clinical Reporting

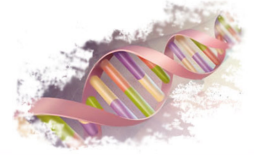
Module 4: Clinical Cases

Plan to develop into Podcasts



Clinical sequencing pilot study: 400 children from 3 provinces

Analysis and
Interpretation



Alberta
Children's
HOSPITAL



CHU Sainte-Justine
Le centre hospitalier
universitaire mère-enfant

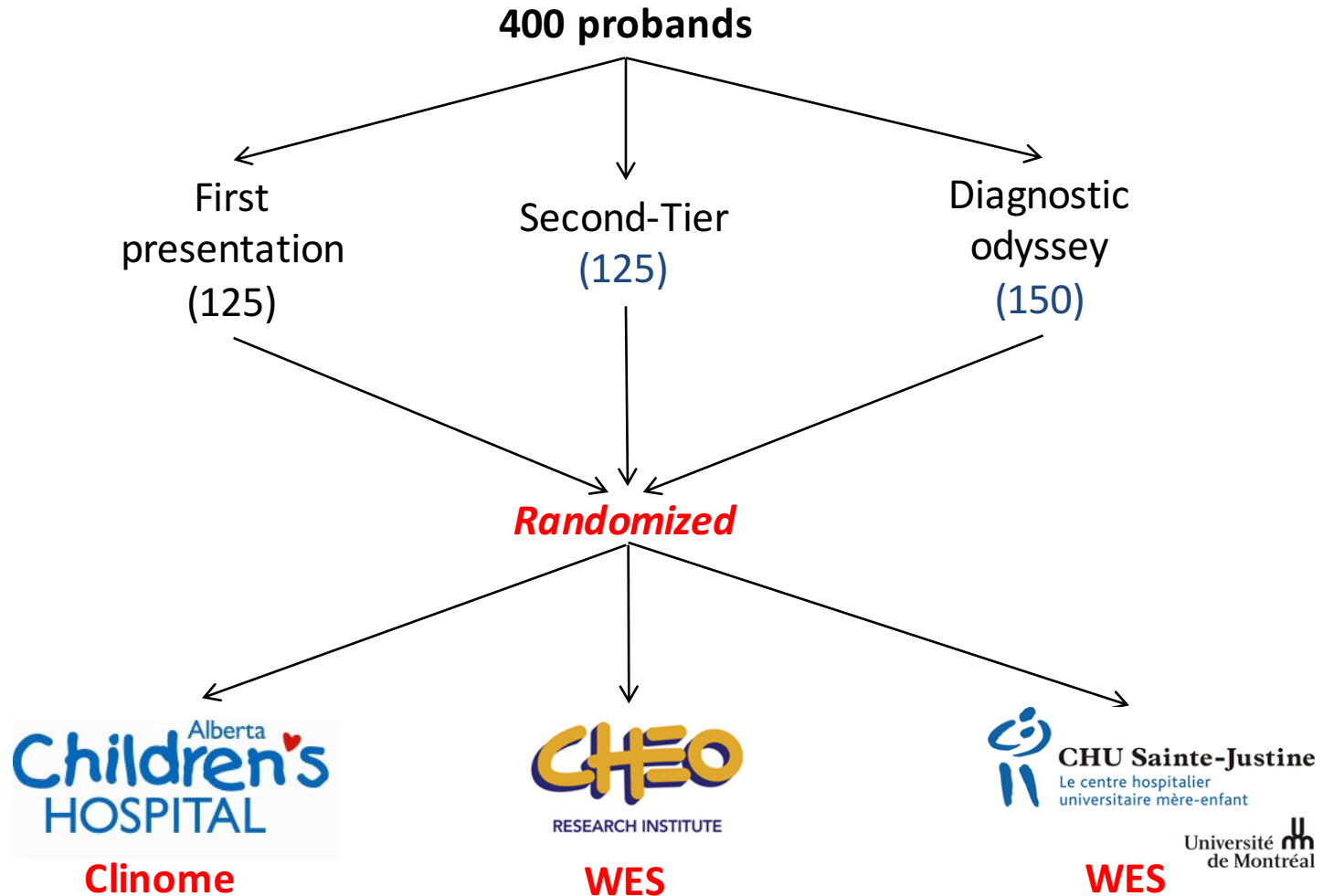
Université 
de Montréal

CHFO

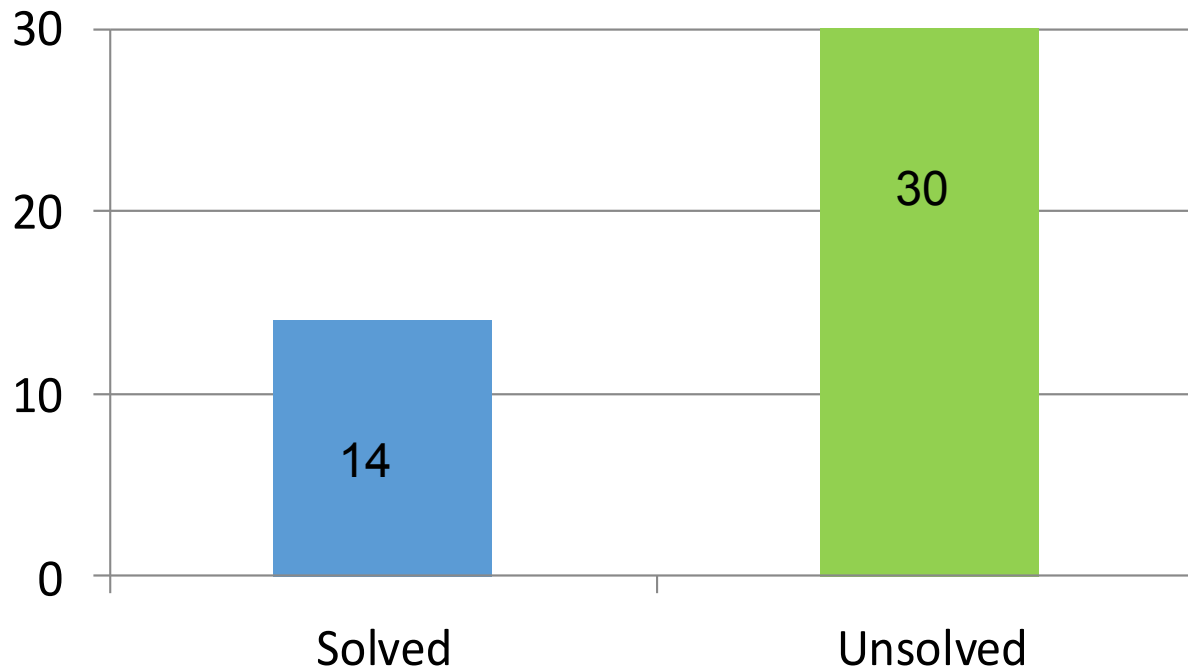


CARE
for**RARE**

C4R activity 2a



C4R activity 2a: Clinome



C4R activity 2a: Clinome

CATEGORY 1: Initial presentation

> 3 genes on differential

2/5 (40%)

CATEGORY 2: Second-tier testing

Follow-up appointment, first investigations normal

6/15 (40%)

CATEGORY 3: Diagnostic odyssey

No diagnosis following standard-of-care

6/24 (20%)

Diagnostic translation

Tools and
Guidelines



OPEN ACCESS

ORIGINAL ARTICLE

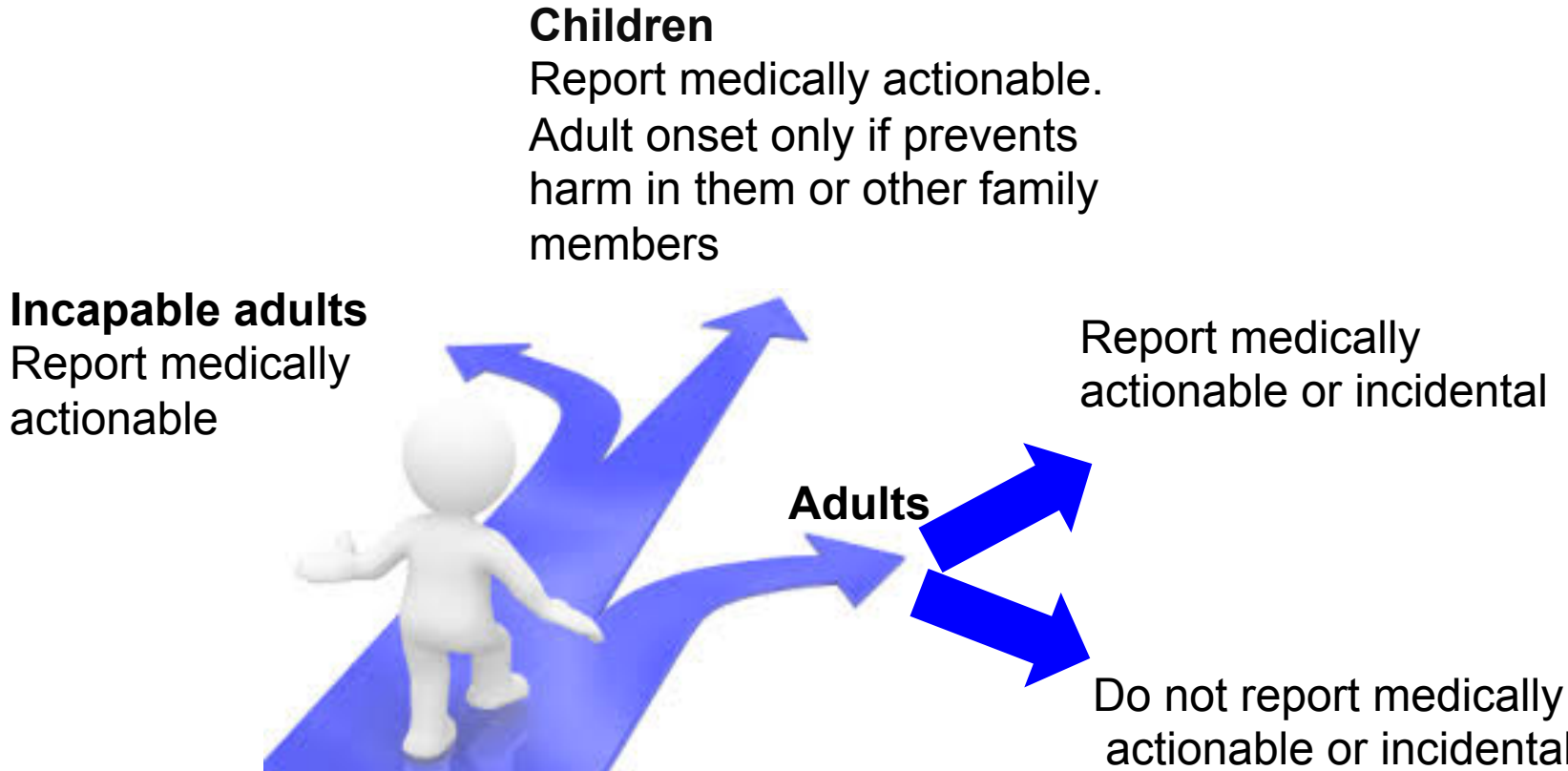
The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists

Kym Boycott,¹ Taila Hartley,¹ Shelin Adam,² Francois Bernier,³ Karen Chong,^{4,5} Bridget A Fernandez,⁶ Jan M Friedman,² Michael T Geraghty,¹ Stacey Hume,⁷ Bartha M Knoppers,⁸ Anne-Marie Laberge,⁹ Jacek Majewski,¹⁰ Roberto Mendoza-Londono,⁴ M Stephen Meyn,^{4,11} Jacques L Michaud,⁹ Tanya N Nelson,¹² Julie Richer,¹ Bekim Sadikovic,¹³ David L Skidmore,¹⁴ Tracy Stockley,¹⁵ Sherry Taylor,⁷ Clara van Karnebeek,² Ma'n H Zawati,⁸ Julie Lauzon,³ Christine M Armour,¹ on behalf of the Canadian College of Medical Geneticists

Journal of Medical Genetics 2015

Canadian Guidelines: Primary indication is the focus

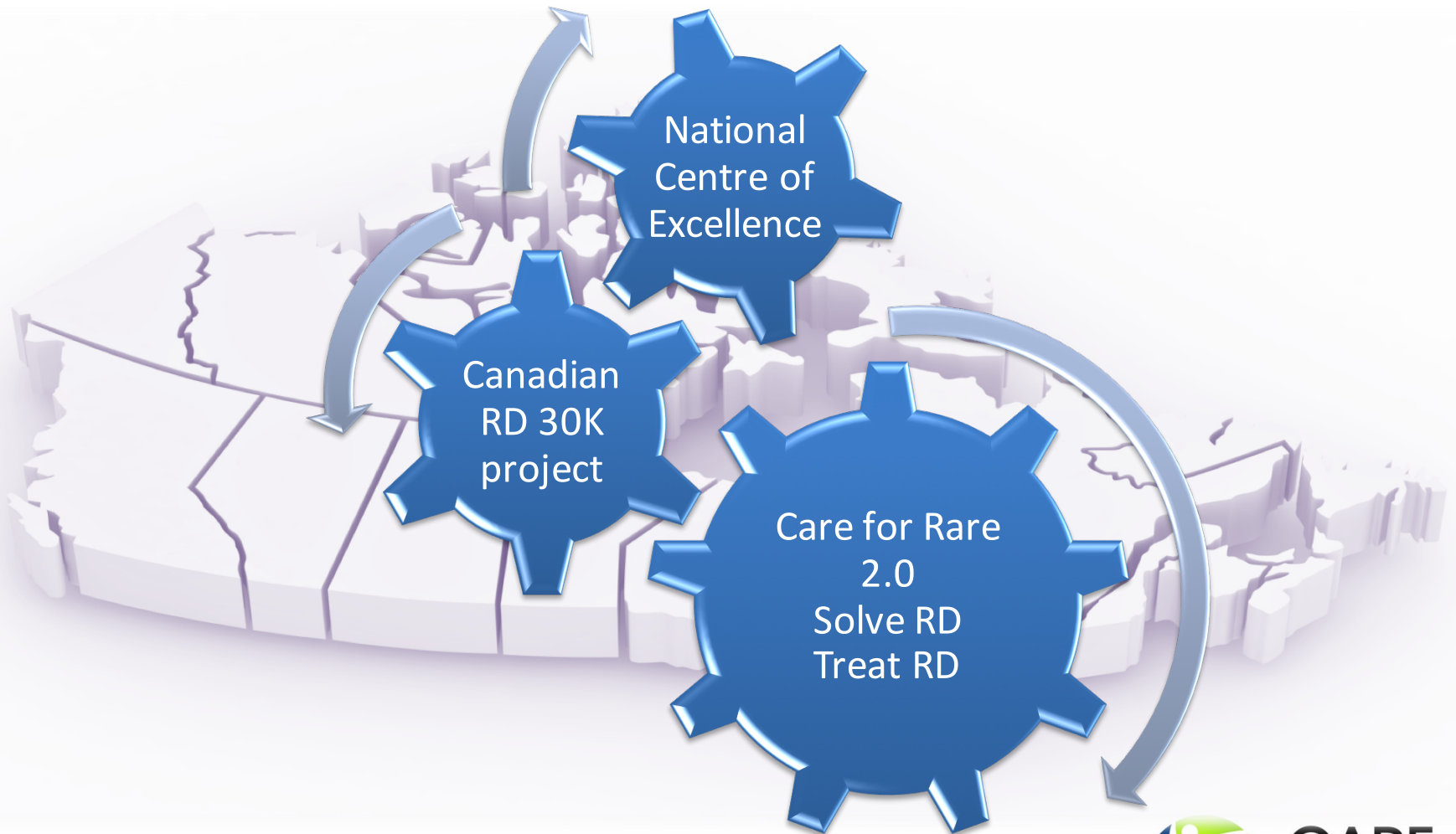
Approach to Incidental Findings



Boycott et al., JMG 2015



Care for Rare Next Steps





GenomeCanada



CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

CHEO Research Institute
Institut de recherche

Alberta
Children's HOSPITAL
RESEARCH INSTITUTE



Ontario **Genomics** Institute
The Future is in Our Genes.



GenomeQuébec



CARE
for **RARE**