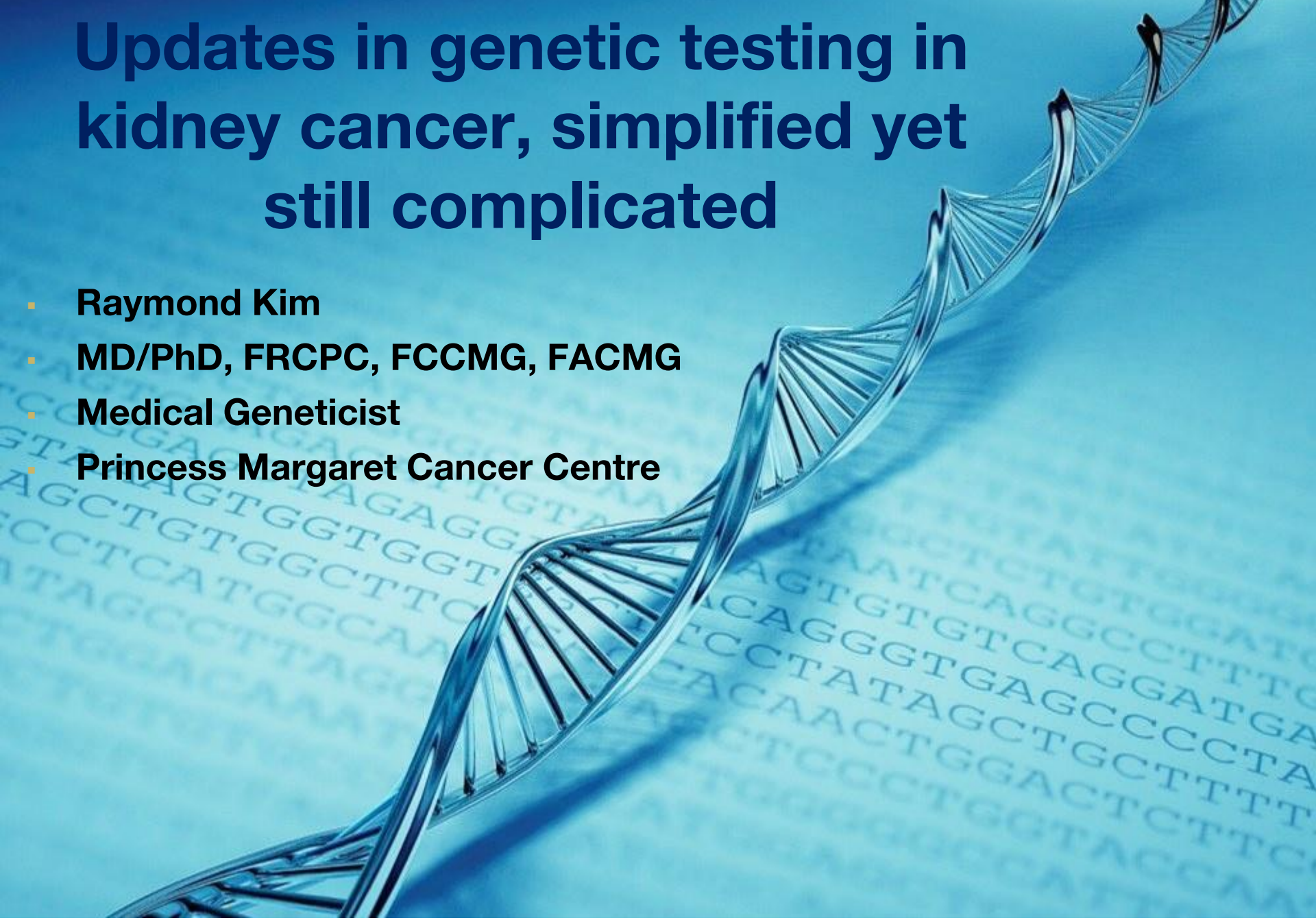
Updates in genetic testing in kidney cancer, simplified yet still complicated

- Raymond Kim
- MD/PhD, FRCPC, FCCMG, FACMG
- Medical Geneticist
- Princess Margaret Cancer Centre



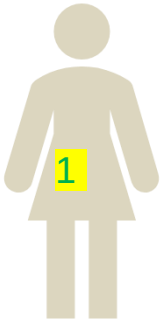
UHN Princess Margaret Cancer Centre

No disclosures

Sporadic cancer (90%)

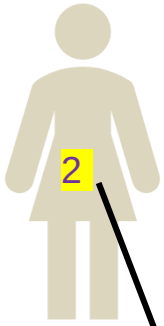
1st hit

life



2nd hit

life

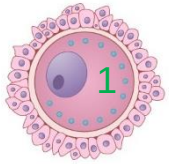


-No other tissues have mutation
-Blood testing no mutations

"normal" genes at birth

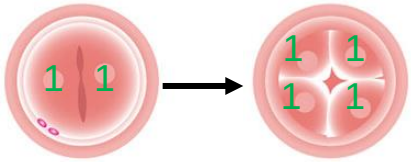
Two hits tumour growth, (all cancers*)

Hereditary cancer (10%)



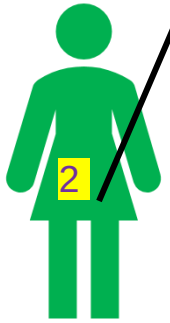
or

born with mutation



2nd hit

life



-All tissues have first mutation
-at risk of more cancers

Blood testing mutation detected

Family tree with a pattern
Unusual tumours
Multiple cancers in same individual
Young cancers ~10 years earlier

Could my patient's kidney cancer be hereditary?

- Young kidney cancer (<45 or 50 years)
- Strong family history of cancer (especially kidney)
- Another cancer
- Kidney cancer in both kidneys
- Multifocal tumours
- Rare histology

KCRNC | RRCRC
KIDNEY CANCER RESEARCH NETWORK OF CANADA | RÉSEAU DE RECHERCHE SUR LE CANCER DU REIN DU CANADA

- All need genetic testing
- Awareness is low

Table 2: Criteria for referring patients with renal tumours for genetic assessment

1. Patients with any renal tumour (benign or malignant) AND any one of the following:
   a. **Bilaterality** or **multifocality**
   b. **Early age of onset** (≤45 years of age)
   c. **1st or 2nd degree relative** with any renal tumour
   d. A history of **pneumothorax***
   e. One of the following **dermatologic findings**:
      i. Skin leiomyomas*
      ii. Skin fibrofolliculomas/trichodisomas*
   f. One of the following **associated tumours**:
      i. Pheochromocytoma/paraganglioma*
      ii. Hemangioblastoma of the retina, brainstem, cerebellum or spinal cord*
      iii. Early onset of multiple uterine fibroids (<30 years of age)*
   g. Lymphangiomyomatosis*
   h. Childhood seizure disorder*
   (*or 1st degree relative with same)
2. Patients with **non-clear cell** carcinoma with unusual associated features (e.g., chromophobe, oncocytic or hybrid tumours)
3. Patients, with or without RCC, who report a family member (any) with a known **clinical or genetic diagnosis** of any one of the following:
   a. Von Hippel-Lindau syndrome
   b. Birt-Hogg-Dubé syndrome
   c. Hereditary leiomyomatosis and renal cell cancer
   d. Hereditary papillary renal cell cancer
   e. Hereditary paraganglioma/pheochromocytoma
   f. Tuberous sclerosis

Reaume 2013

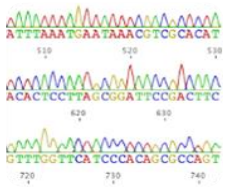
Traditional Model of Genetic testing

Physician identification and Referral

Pre-Test Counselling

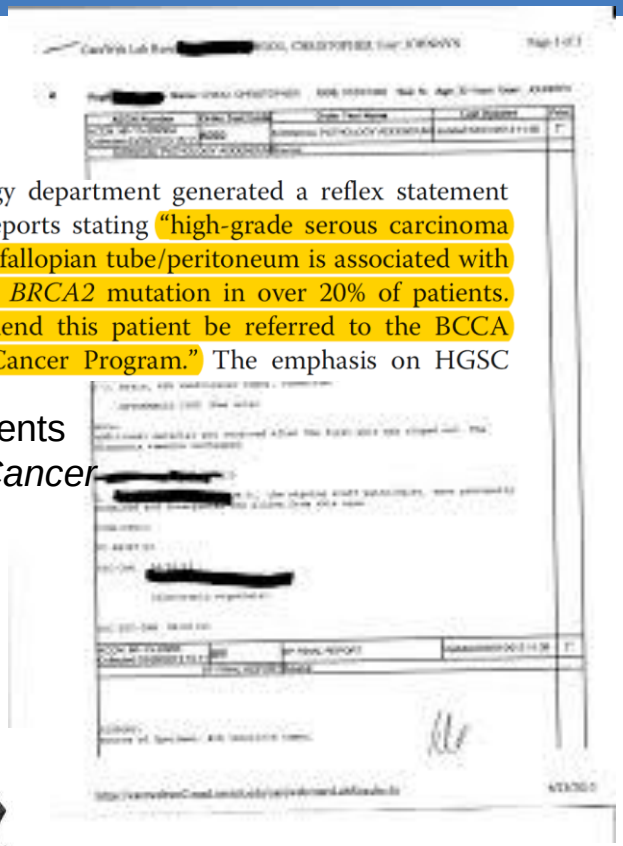
Blood Draw

Results



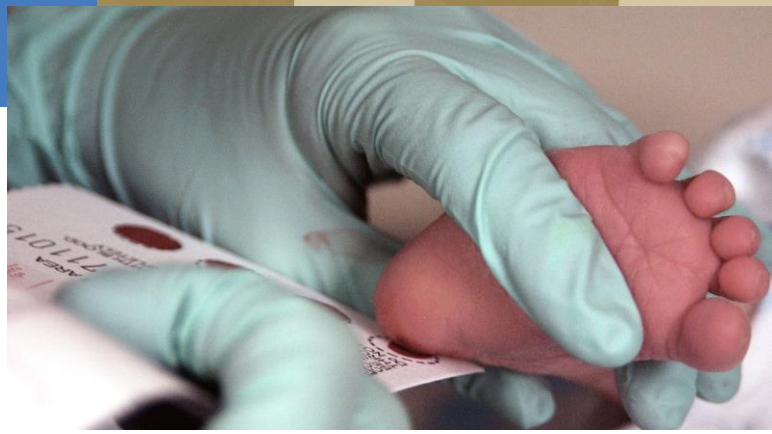
Months -years

Strategies to increase awareness



our pathology department generated a reflex statement with their reports stating "high-grade serous carcinoma of the ovary/fallopian tube/peritoneum is associated with a *BRCA1* or *BRCA2* mutation in over 20% of patients. We recommend this patient be referred to the BCCA Hereditary Cancer Program." The emphasis on HGSC

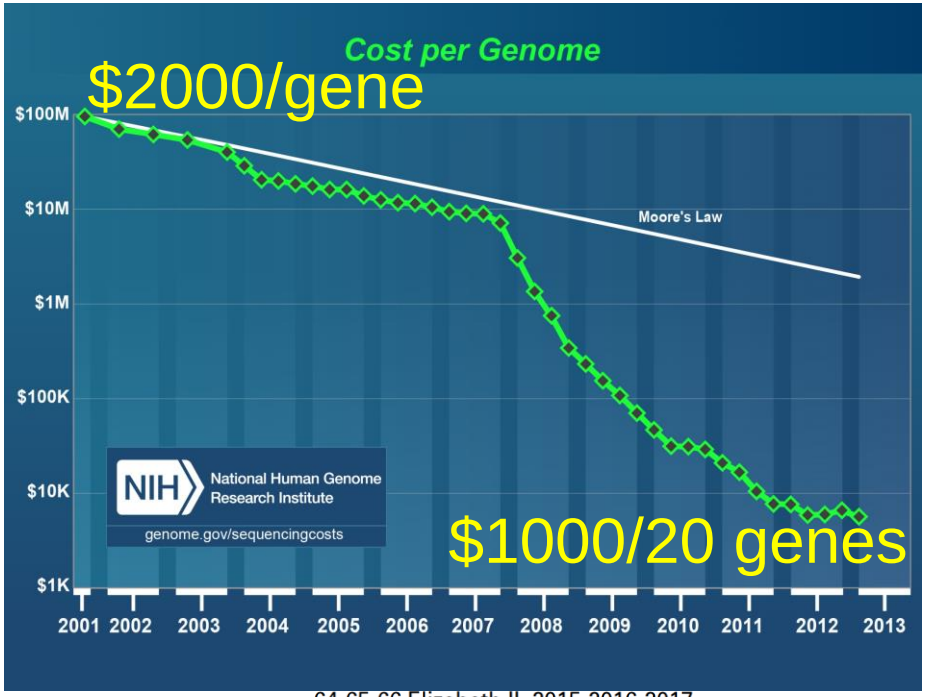
Reflexive pathology statements
Hanley et al. (2018) *BMC Cancer*



Opt-out Genetics Referral
McGee et al. (2017) *Int J Gynecol Cancer*

Genetics at Tumour Boards
Cohen et al (2016) *Int J Gynecol Cancer*

Increasing Demand



64-65-66 Elizabeth II, 2015-2016-2017

STATUTES OF CANADA 2017

CHAPTER 3

An Act to prohibit and prevent genetic discrimination

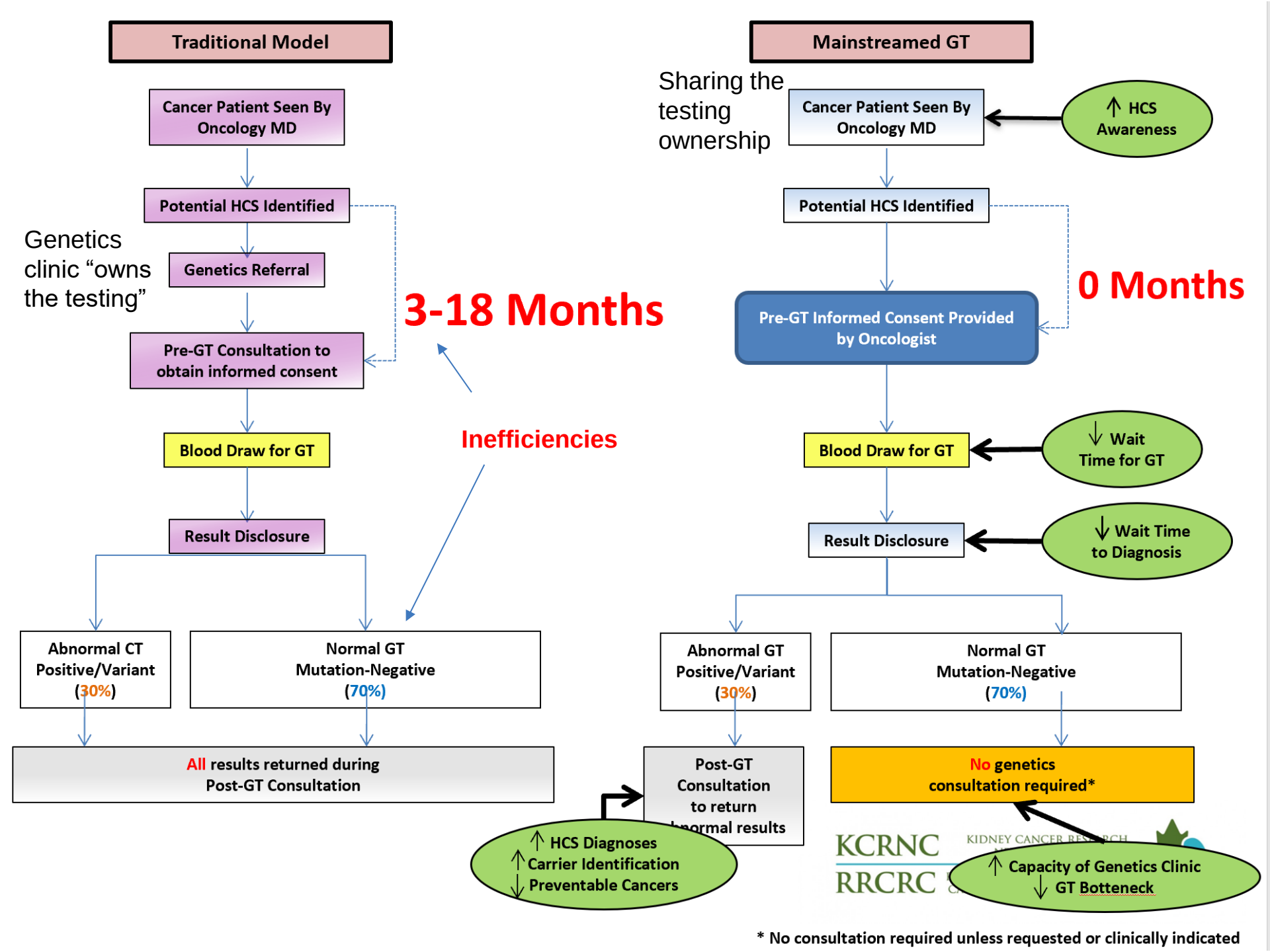
ASSENTED TO

MAY 4, 2017

BILL S-201

Genetics Non-discrimination Act (GNA)

- Providers of goods and services (including insurance-disability and life) cannot:
  - Request a person undergo genetic testing
  - Request disclosure of previous or future genetic testing results
- Federally regulated employers cannot:
  - Request or require genetic test results of an employee
  - Use a person's genetic test results in decisions about hiring, firing, job assignments or promotions
- Unlike US GINA, does not protect from family history


Traditional Model
Cancer Patient Seen By Oncology MD
Potential HCS Identified
Genetics Referral
Genetics clinic "owns the testing"
Pre-GT Consultation to obtain informed consent
3-18 Months
Blood Draw for GT
Inefficiencies
Result Disclosure
Abnormal CT Positive/Variant (30%)
Normal GT Mutation-Negative (70%)
All results returned during Post-GT Consultation
Mainstreamed GT
Sharing the testing ownership
Cancer Patient Seen By Oncology MD
↑ HCS Awareness
Potential HCS Identified
0 Months
Pre-GT Informed Consent Provided by Oncologist
Blood Draw for GT
↓ Wait Time for GT
Result Disclosure
↓ Wait Time to Diagnosis
Abnormal GT Positive/Variant (30%)
Normal GT Mutation-Negative (70%)
Post-GT Consultation to return abnormal results
No genetics consultation required*
↑ HCS Diagnoses
↑ Carrier Identification
↓ Preventable Cancers
KCRNC
RRCRC
KIDNEY CANCER RESEARCH
↑ Capacity of Genetics Clinic
↓ GT Botteneck
* No consultation required unless requested or clinically indicated

Canadian versions of BRCA1/2 Mainstreaming

BC CANCER

GENONC

GOBRCA

Institution-specific

Centre universitaire de santé McGill — McGill University Health Centre

Alberta Health Services

ONCOGENE

UHN Princess Margaret Cancer Centre

Northwest Territories
Nunavut
British Columbia
Alberta
Saskatchewan
Manitoba
Ontario (North)
Ontario (South)
Quebec
Newfoundland and Labrador
Prince Edward Island
Nova Scotia
New Brunswick

Mainstreaming kidney cancer-Ontario Pilot

- Oncologists orders genetic testing (non-geneticist)
- Young kidney cancer (<45 years)
- Bilateral and multifocal Kidney cancer
- Non-ccRCC
  - Chromophobic (FLCN, PTEN)
  - Oncocytic (FLCN)
  - Papillary type 1 (MET)
  - Papillary type 2 (FH)

Mainstreaming kidney cancer-Ontario Pilot

- Brief consent by Oncologist

- 18 Gene panel
- Toronto UHN Lab Provincially funded
- *BAP1*, CDC73, DICER1, FH*, FLCN*, MET, MITF, PTEN*, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TP53, TSC1*, TSC2*, VHL*

- 70% will be normal, never need to see genetics
- 30% abnormal and will need to see genetics

- Who is ordering: Tony Finelli, Rob Hamilton, Nathan Perlis, Aaron Hansen
- Roll out to other sites (London, Hamilton, Ottawa)
- Integration with CKCiS

What is a gene?

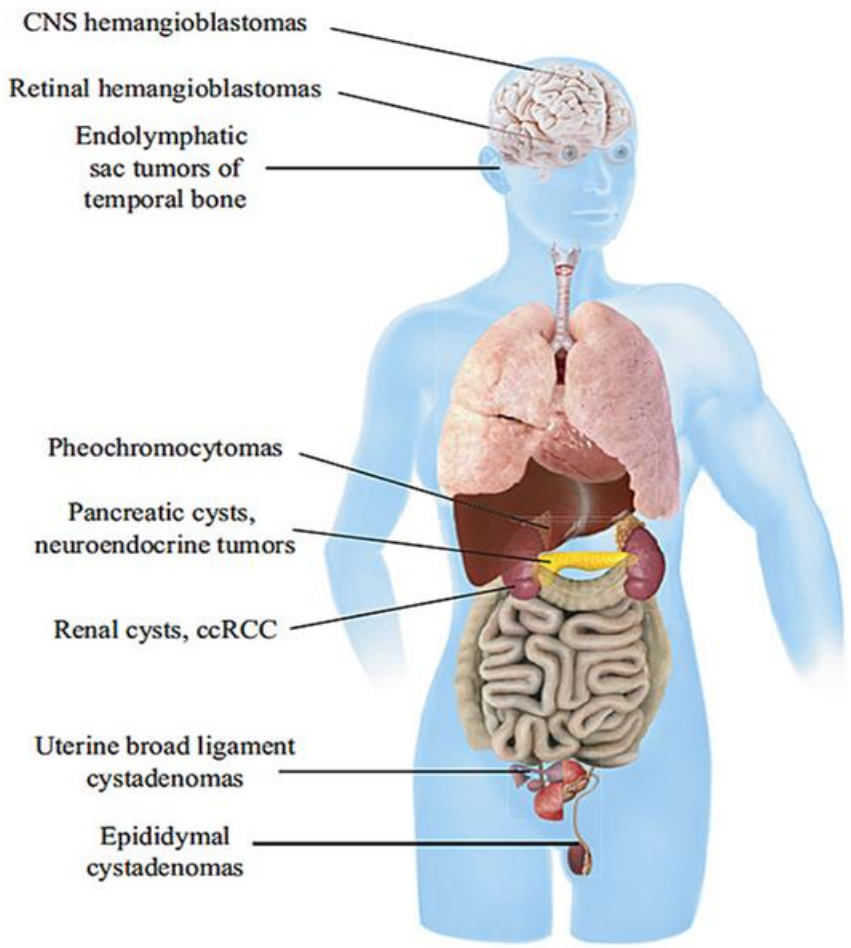
Genes are pieces of your DNA. Your DNA is found inside every cell in your body. Your genes tell your body how to work.

Each gene has a role in your body. Some genes affect traits like your hair colour, eye colour and height. Other genes affect your risk for certain diseases, like cancer.

You get your genes from your parents. Half of your genes are from your mom. The other half of your genes are from your dad.

ccRCC, Von Hippel Lindau

- Multi-system disorder
- Mutations in *VHL* gene responsible for degradation of hypoxia inducible factor 1-alpha (HIF1α)
- Results in hemangioblastomas
  - Eye
  - Brain
  - Spine
- Deafness (endolymphatic sac tumours)
- Pancreatic cysts
- variable expressivity = not all mutation carriers develop all manifestations
- Frameshift mutations result in risk of renal cell carcinoma “type 1”
- Missense mutation result in pheochromocytoma “type 2”
- Genetics is not straightforward



Ho & Jonasch

VHL Alliance

UHN Princess Margaret Cancer Centre

VHL Case Studies
Scenario 1: Clinical Case Study

- 23 year old patient with renal cell carcinoma
- Gene panel testing reveals a germline *VHL* variant:
  - c.345C>G [p.H115Q missense mutation]
  - Lab classification: Variant of unknown significance
- Family history is negative for VHL disease
  - No VHL mutations in family members
- Does this patient have VHL disease?
- Should this patient receive life-long surveillance?

VHL Case Studies
Scenario 2: VHL Research

- Researcher wants to know what VHL variants are associated with ccRCC
- Where to look?
  - PubMed
  - Google Scholar
  - Databases
- How to look?
  - ccRCC, kidney cancer, renal cancer etc

Case study Patient Scenario: ClinVar gene database

- Assertion for (*VHL* c.345C>G) mutation is inconclusive on ClinVar, no phenotype described:

NM_000551.3(VHL):c.345C>G (p.His115Gln)

Interpretation

Go to:

Clinical significance:	Uncertain significance
Last evaluated:	Feb 5, 2016
Number of submission(s):	1

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

Submitter	Allele origin	Individuals	Phenotypes (Affected status)	Ethnicity	Geographic origin	Citations	Description
Integrated Genetics/Laboratory Corporation of America	germline	not provided	not provided (unknown)	not provided	not provided	PubMed	not provided

Classifying Genetic Variants

- The American College of Medical Genetics and Genomics (ACMG) developed rules to determine the medical relevance of a genetic variant
  - Requires certain info about the genetic variant (e.g. population frequency, disease segregation, gene function ***etc***.)
  - Severe (pathogenic) or benign (harmless)
  - 30% of panel testing results are uncertain, and difficult to make medical decisions on such “private variants”

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

How to overcome this?

- Share information about gene variants
- Share information about families

- To reach statistical and genetic significance to call a gene variant benign or severe (pathogenic)

- Large gene-based consortium
- BRCA1/2 (ENIGMA)
- Cystic fibrosis
- Hereditary Colon Cancer (INSIGHT)

- No consortium for any kidney cancer genes

VISION

VHL Information-Sharing International cONsortium

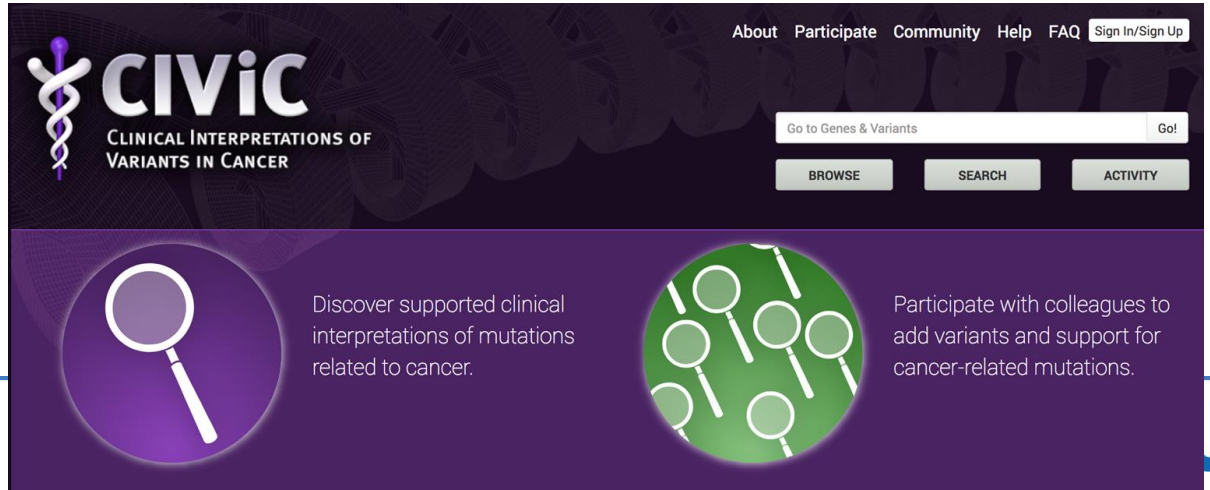
Mandate: Improve VHL disease understanding and treatment on a global scale by sharing genomic and clinical information.

Projects:

- Curate a database of VHL variants
- Establish an Expert Panel to:
  1. Create rules for VHL variant interpretation
  2. Use VHL rules to identify pathogenic variants
- Freely share data with the VHL community around the world

Housing *VHL* Variants in CIViC

- VHL information is scattered and unorganized
- Open access, community-driven web resource for Clinical Interpretation of Variants in Cancer
- Standardized (Human Phenotype Ontology)
- Centralized, debated, and interpreted data of associations between specific mutations, phenotypes, and responses to a targeted therapy
- Search by variant, phenotype, disease, therapy



Assembling all VHL cases ever published

5068 Articles

Information Specialist optimized search to identify VHL publications

- Remove duplicates & untranslated articles

3833 Unique Articles

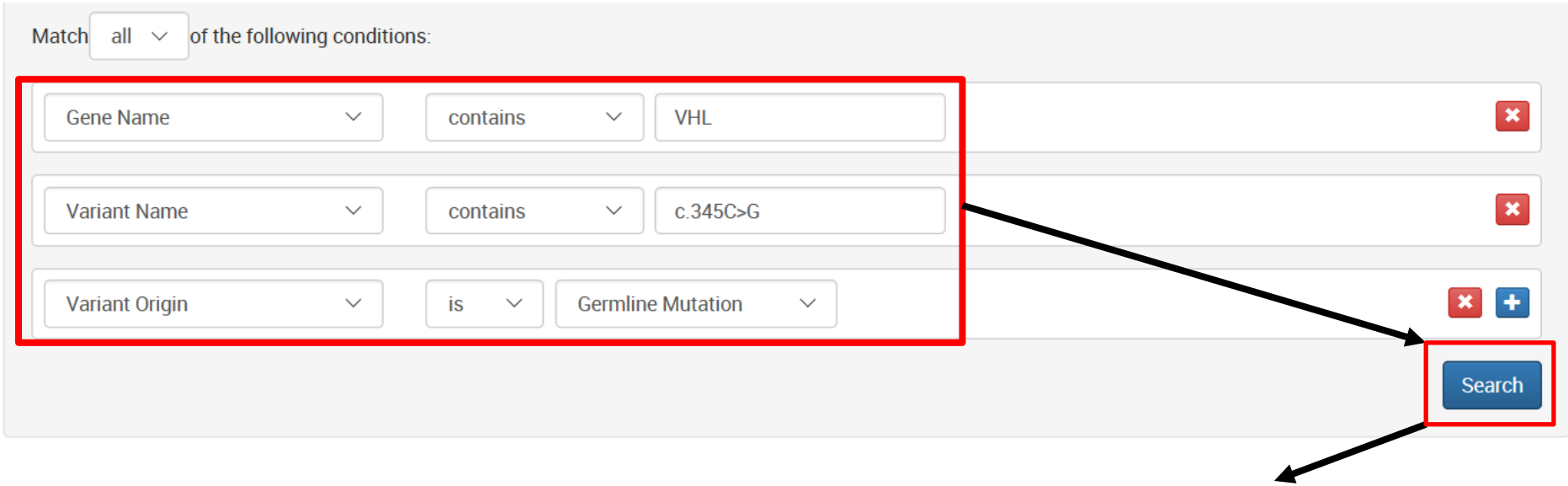
- Remove articles that do not report VHL mutations
- Remove publications with identical patients (⬇ 'double-counting')
- Remove non-human studies (e.g. canine/rodent studies)

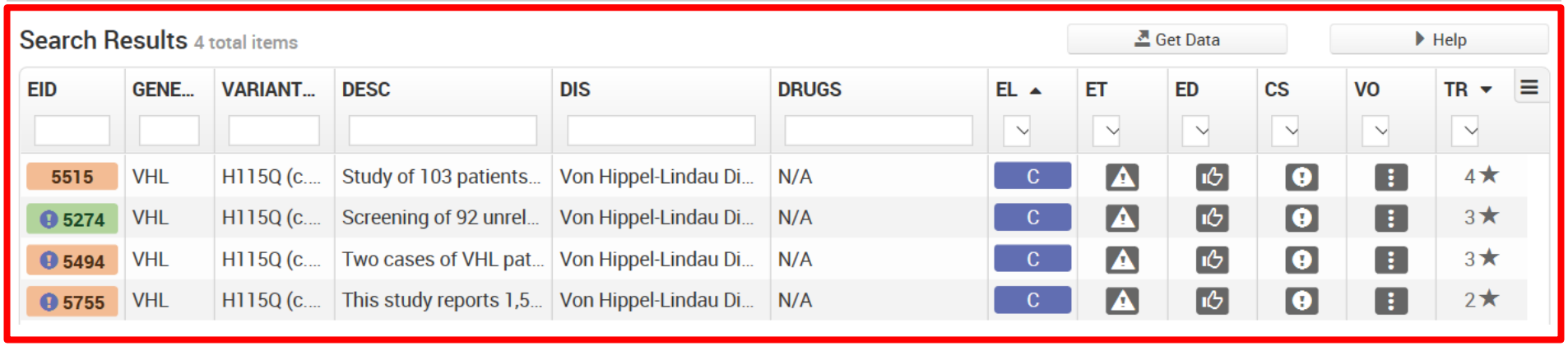
300 Useful Articles (1100 screened)

- Record family history and age of disease onset
- Extract patient genotypes and manifestations
- Standardize mutation coordinates and nomenclature
- Convert phenotypes to standardized HPO terms

2000 cases of VHL → **1324** Evidence statements → **420** Unique VHL variants

Back to the case, c.345C>G
CIViC: Search By Variant





Case Study: Conclusion

- CIViC Evidence Supports c.345C>G Pathogenicity
- Ask lab to reclassify, pathogenic a severe variant

Management decision: Patient should undergo surveillance and likely has VHL disease

Why was it not in ClinVar?

- ClinVar database quality

 Single submitter

 Expert Panel

NM_000551.3(VHL):c.345C>G (p.His115Gln)

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VHL ClinGen Expert Panel

Creating Customized VHL-specific Rules


Eamonn Maher


Tina Pesaran


Carrie Horton

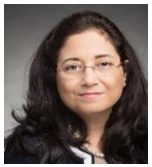

Jerry Machado

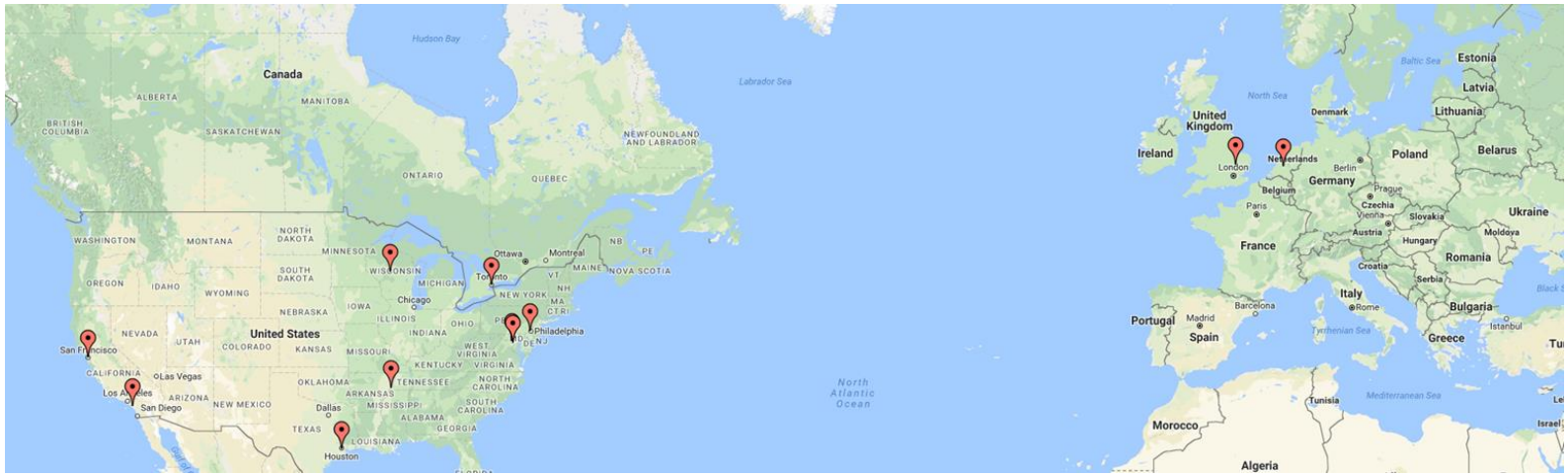

Deborah Ritter


Malachi Griffith


Raymond Kim


Minjie Luo

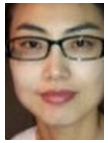

Chimene Kesserwan

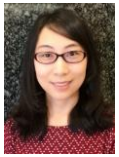



Amit Tirosh

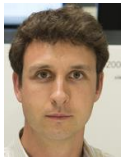

Sharon Plon


Kathleen Hruska


Hio Chung Kang


Ying Wang


Rachel Giles


Obi Griffith

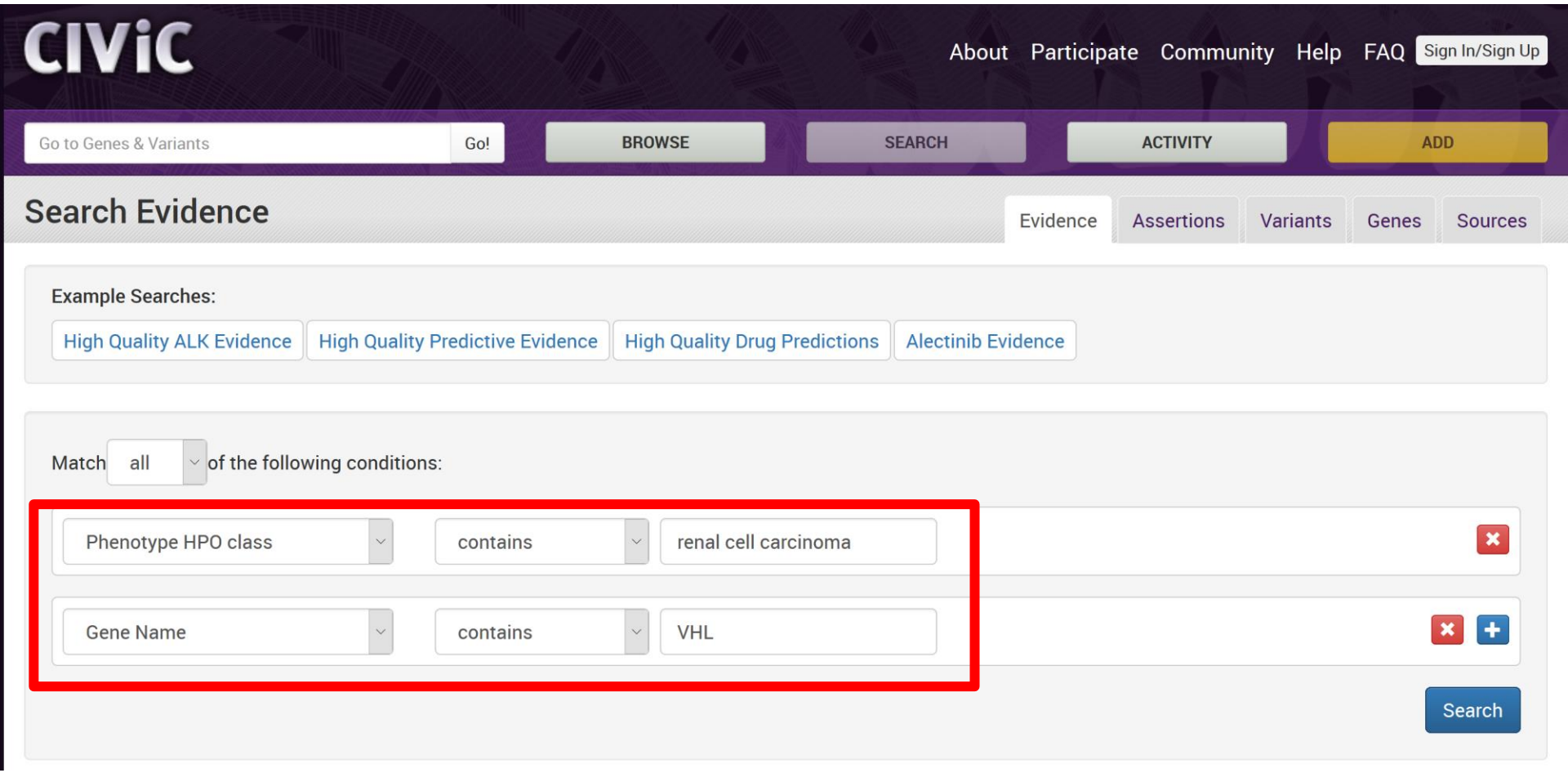

Kilannin Krysiak


Michael Anderson


Kelly McGoldrick

UHN Princess Margaret Cancer Centre

Back to the researcher: CIViC: Search By Phenotype



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CIViC: Search By Phenotype

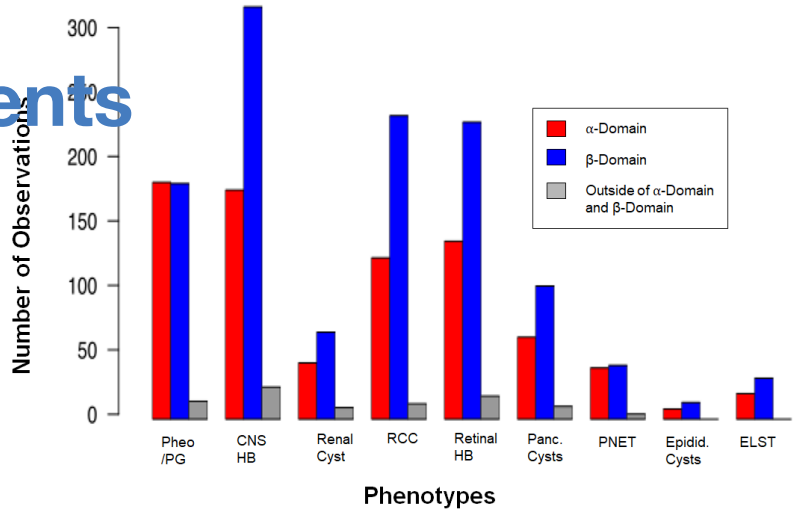
Search Results 421 total items

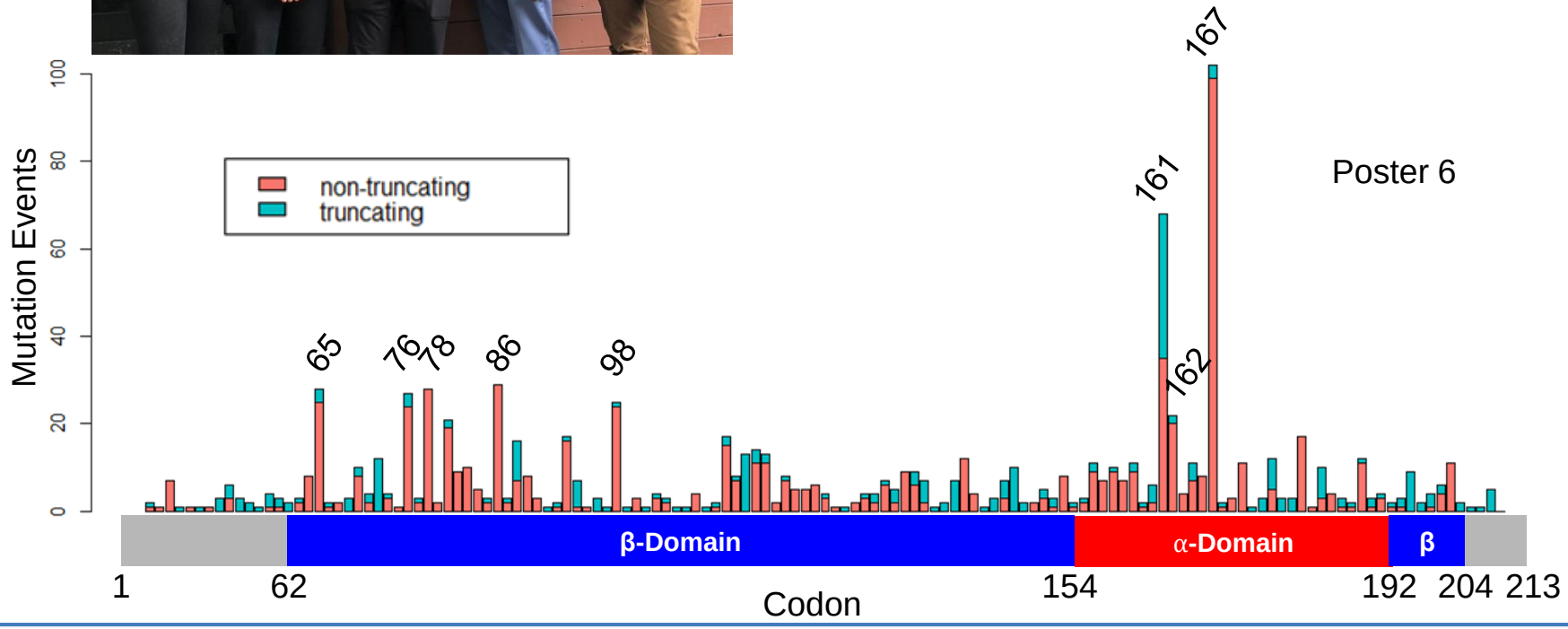
Get Data | Help

EID	GENE	VARIANT	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
5129	VHL	N131T (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	B					4★
6061	VHL	L188Q (c....	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
5169	VHL	W88* (c.2...	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5159	VHL	S65L (c.1...	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5152	VHL	F136S (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5145	VHL	L153C (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5131	VHL	Q132P (c....	Genotype-phenotype ...	Von Hippel-Lindau Di...	N/A	C					4★
5130	VHL	N78H (c.2...	Genotype-phenotype ...	Renal Cell Carcinoma	N/A	C					4★
1942	VHL	EXON 1-3 ...	Mutation detected in ...	Von Hippel-Lindau Di...	N/A	C					4★
5866	VHL	Y112N (c....	This paper analyzes a...	Von Hippel-Lindau Di...	N/A	C					4★
6420	VHL	EXON 1 D...	Molecular analysis of...	Von Hippel-Lindau Di...	N/A	C					4★
4916	VHL	V62C (c.1...	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
4918	VHL	Q73* (c.21...	In a study of 114 unre...	Von Hippel-Lindau Di...	N/A	C					4★
4919	VHL	F76del (c....	This deletion mutatio...	Von Hippel-Lindau Di...	N/A	C					4★

Variants Associated with RCC

CIViC 1324 Evidence Statements





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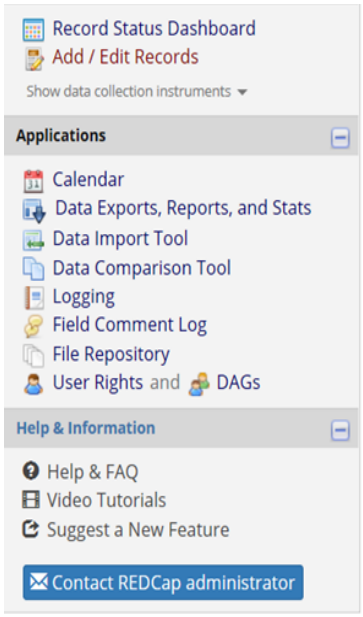
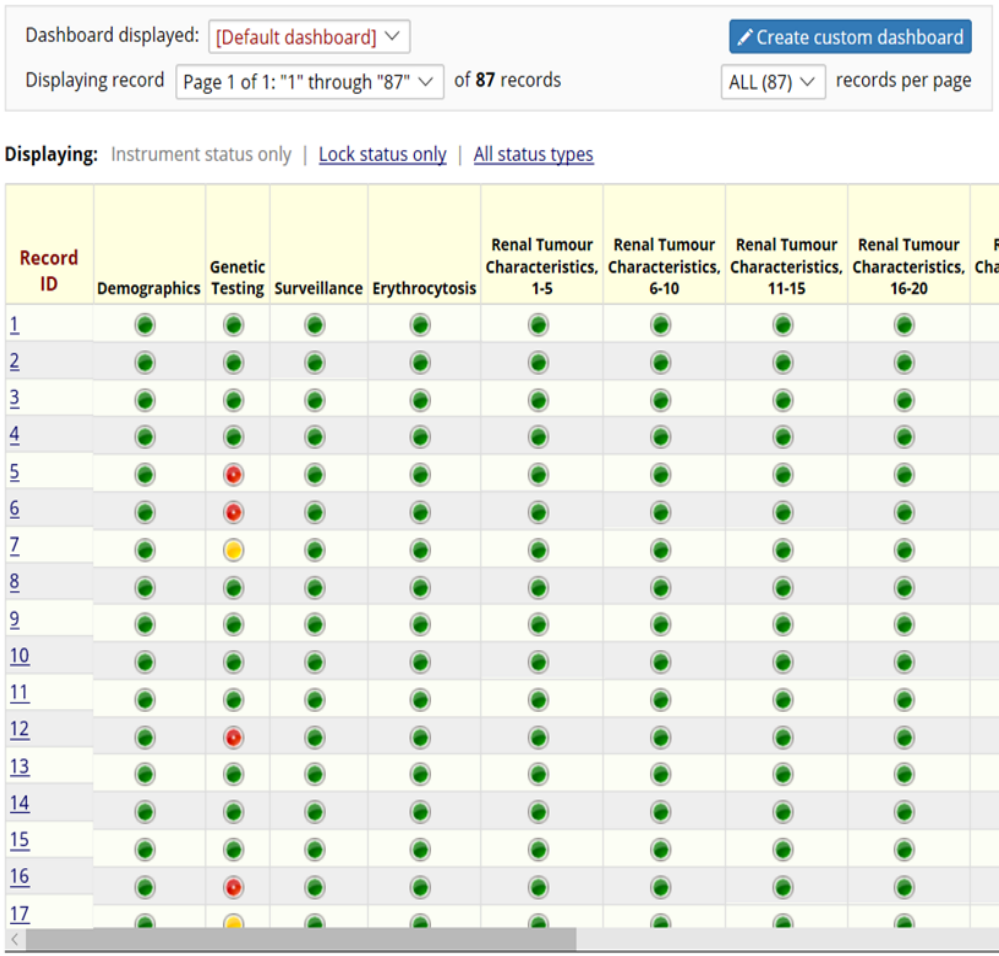
Local VHL populations: REDCap

- CIViC Captures published patients
- VHL disease is a multisystem disease
  - Existing databases only focus on specific manifestations
- Our database captures highly detailed, head-to-toe clinical data
  - Input from Multiple VHL authorities from different organ systems
  - REDCap has 8000 fields!
- Free to use, shareable

REDcap





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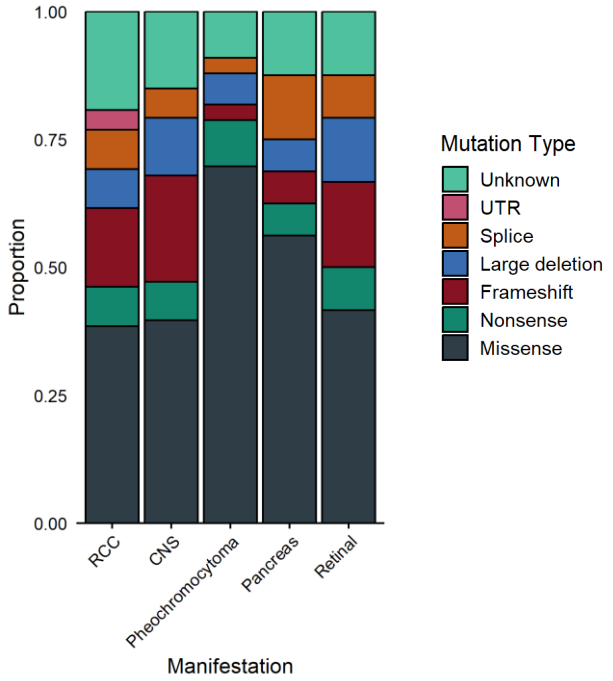
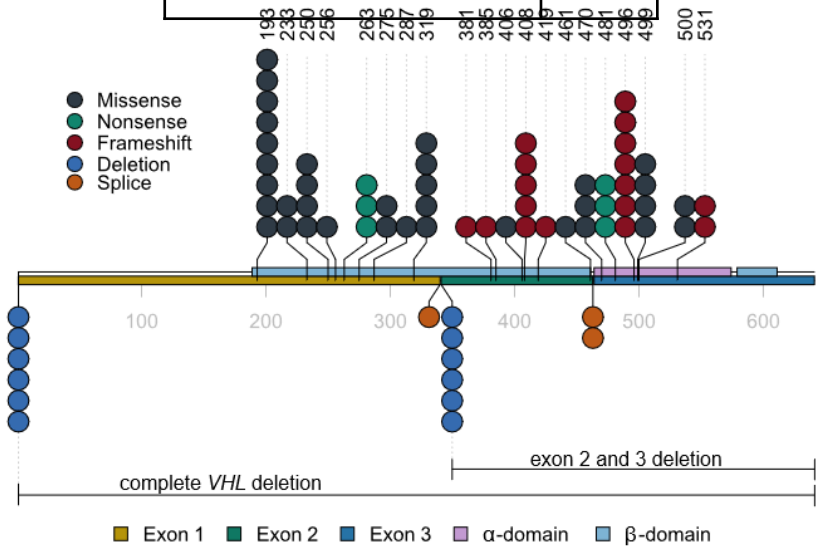
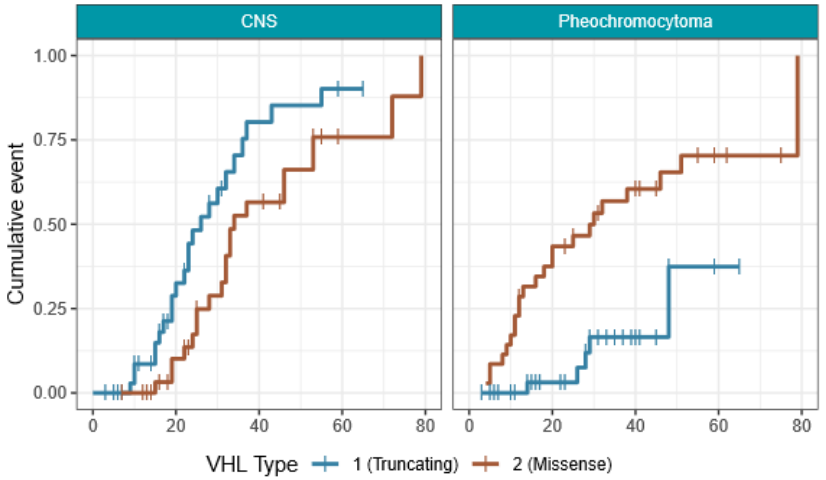
REDcap Data – 88 Toronto pts

Poster 8

	N (%)
Total number of patients	87
Mean Age	35
Mean Age of Genetic Diagnosis	24
Female	54 (62)
Male	33 (38)
Probands	40 (46)
de novo VHL	23 (26)
Genetic Testing	81 (93)
+ VHL[a]	77 (95)
Results unknown[a]	4 (5)
Mutation Type	
Missense[b]	36 (47)
Nonsense[b]	5 (6)
Frameshift[b]	17 (22)
Large Deletion[b]	13 (17)
Intronic/Splice[b]	5 (6)
UTR[b]	1 (1)

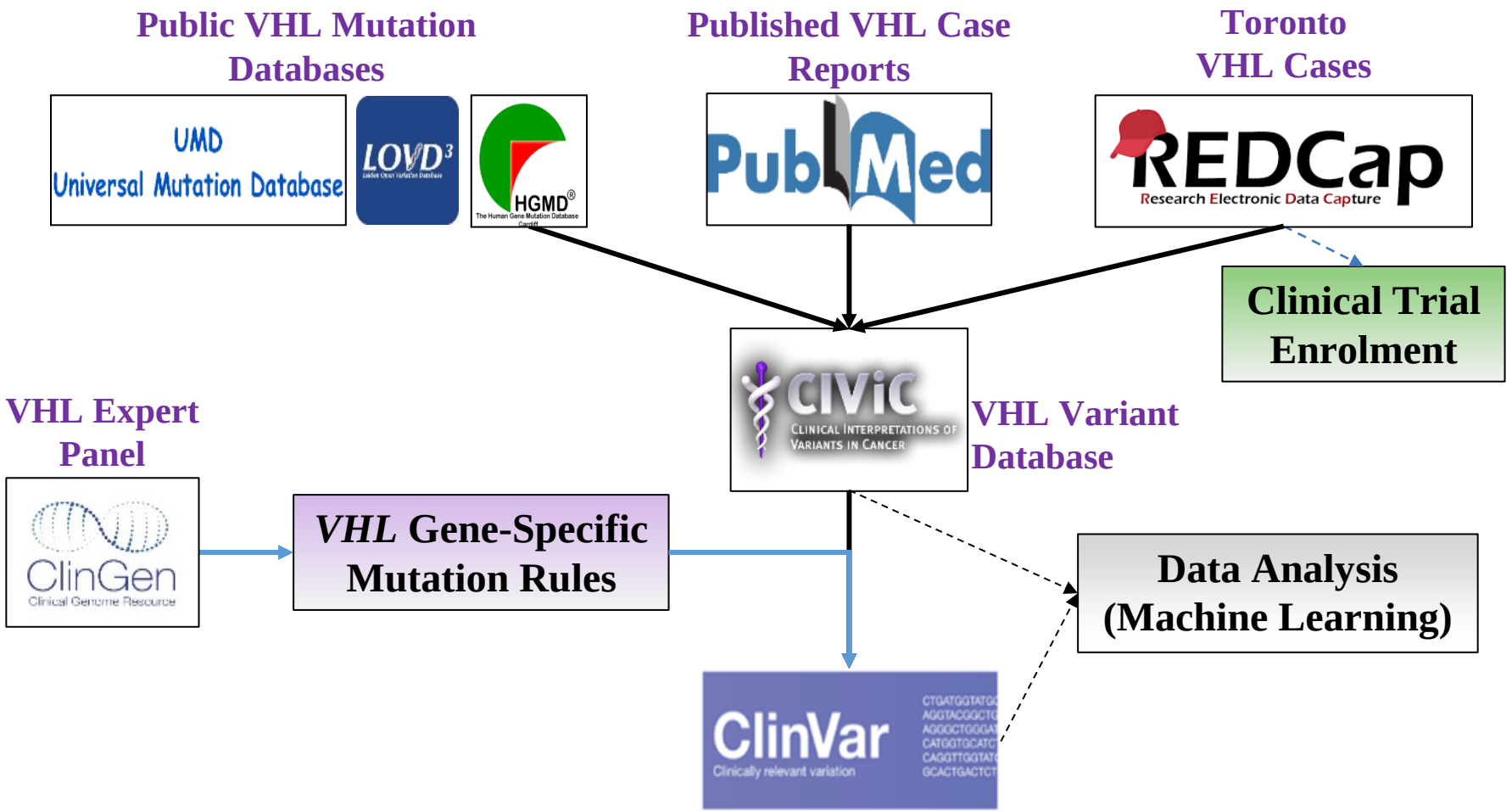






UHN Princess Margaret Cancer Centre

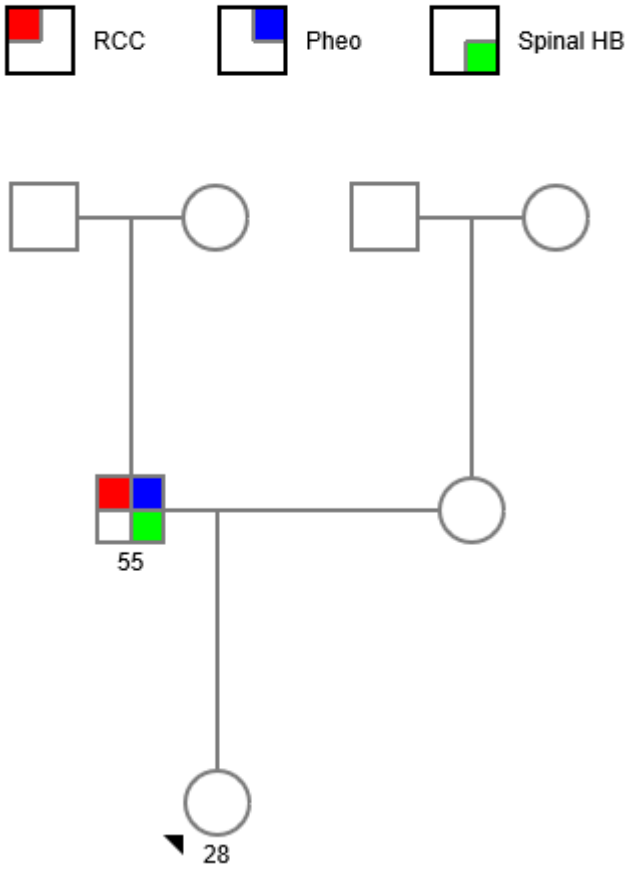
VISION Overview



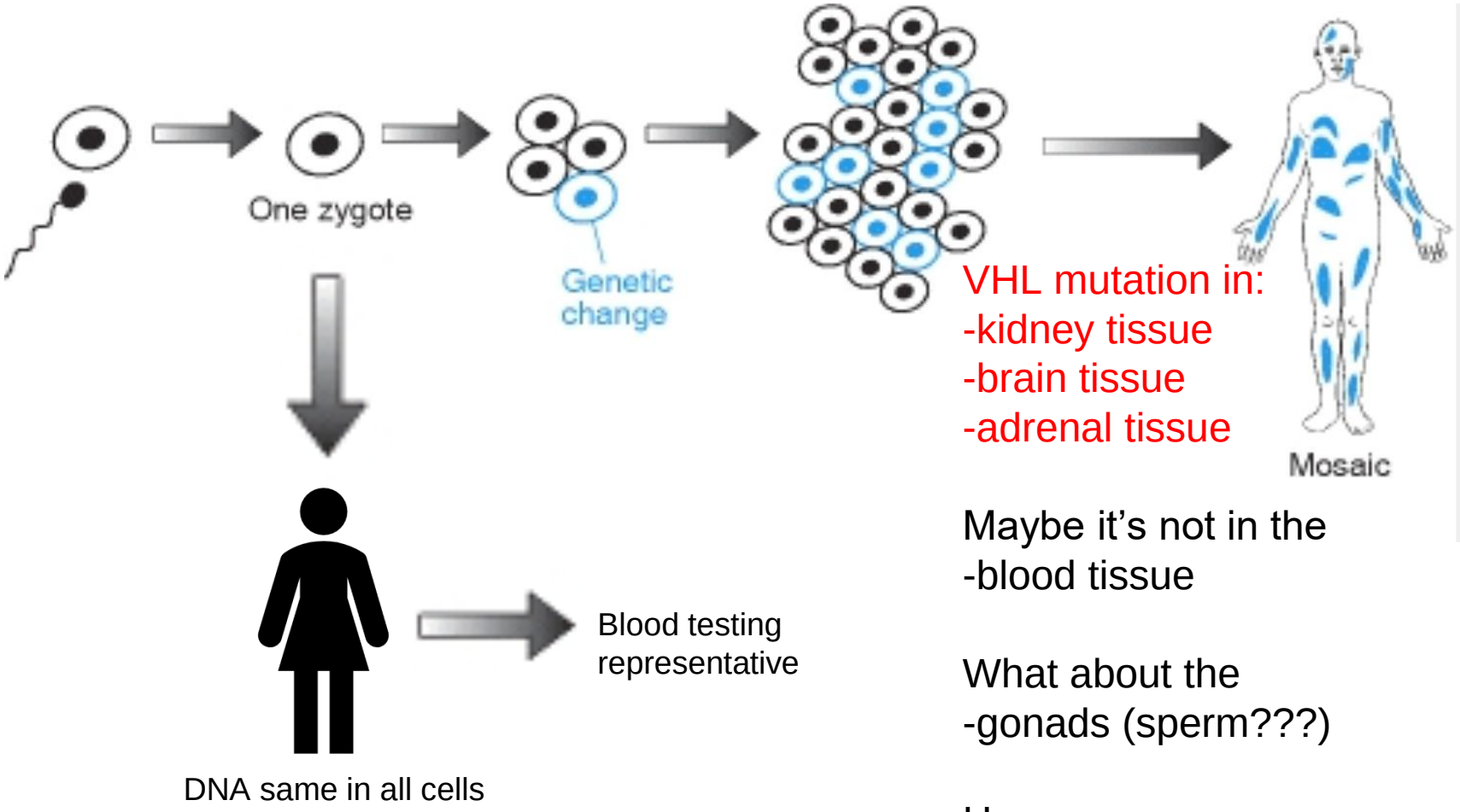
Tough VHL cases gene elusive

- 28-year-old lady referred for a family history of Von Hippel-Lindau syndrome.
- Her father was found to have VHL at the age of 55
- pheochromocytoma, clear cell renal cell carcinoma and hemangioblastoma

- Father's gene panel testing with a renal panel and a paraganglioma panel were negative. (including VHL)
- *VHL* testing in the daughter was also negative.



A mosaicism, a rare genetic phenomenon



VHL mutation in:
-kidney tissue
-brain tissue
-adrenal tissue

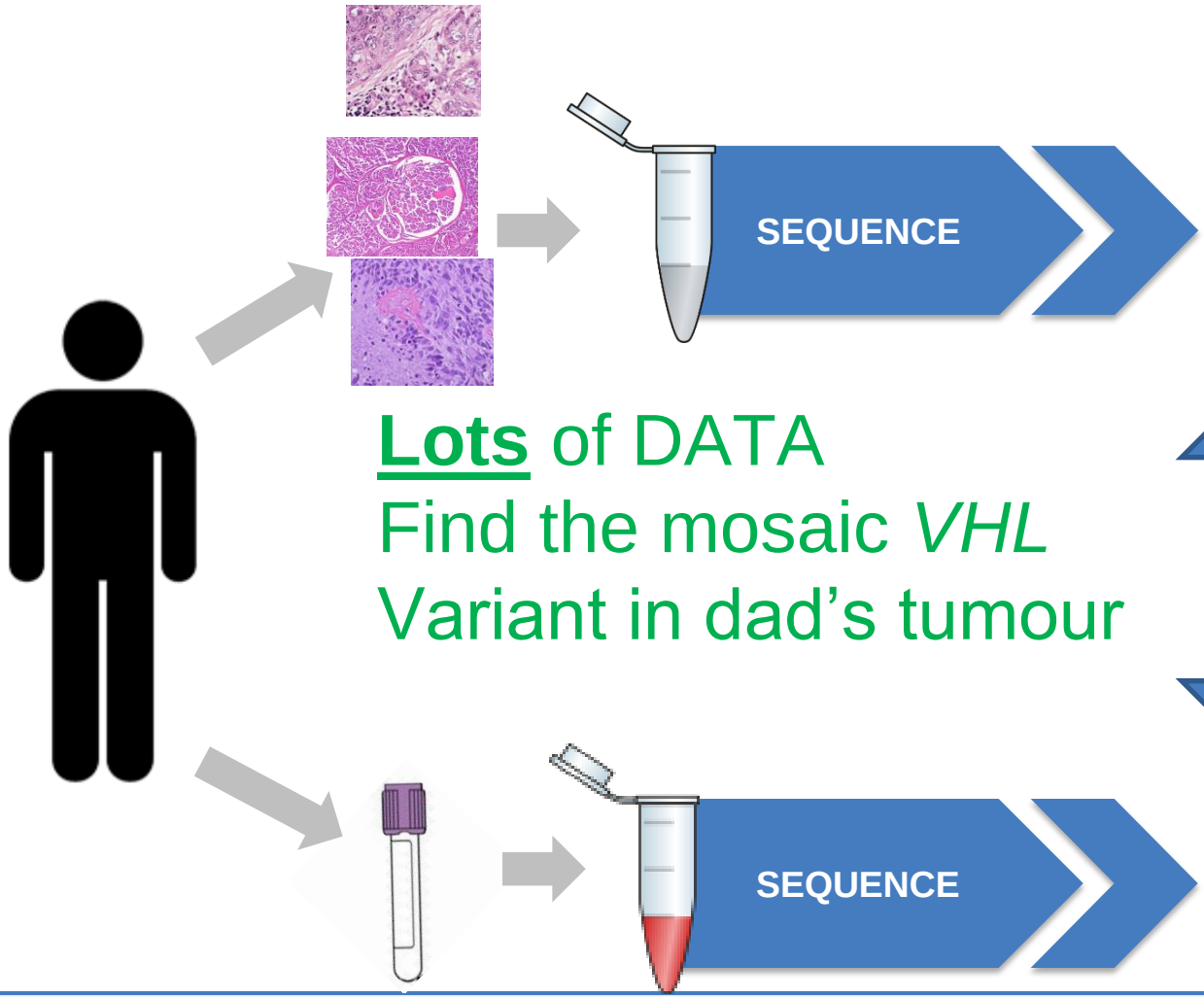
Maybe it's not in the
-blood tissue

What about the
-gonads (sperm???)

How can we answer this?

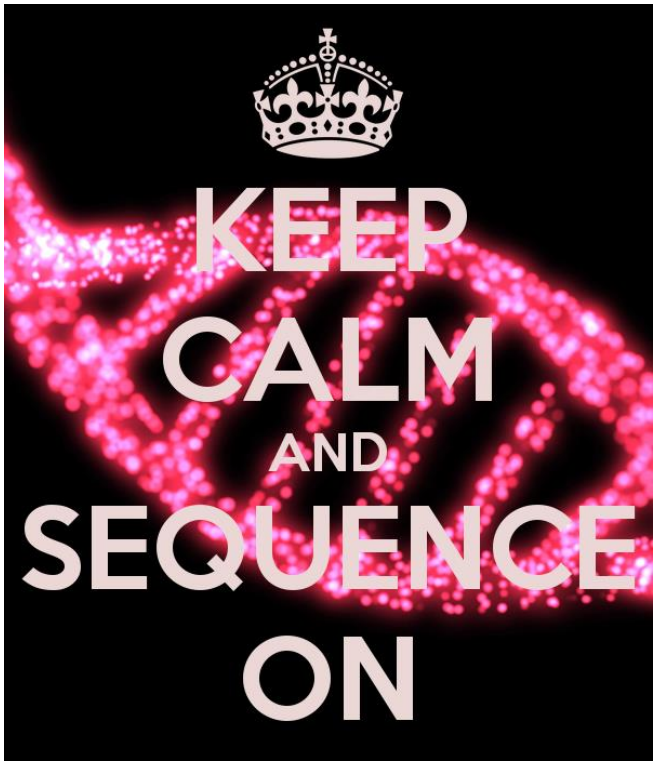
Overcoming the challenges (InSIGHT)

-Integrative Sequencing in Germline and Hereditary Tumours



Summary

- Mainstreaming: Kidney cancer genetic testing is easy to order
- VISION: VHL gene variants need further research
- INSIGHT: Genomics of multiple tissues can answer very challenging kidney cancer cases



raymond.kim@uhn.ca