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Pharmacogenetics: Personalized Medicine for the Masses

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Genetic Counsellor


I'M WORRIED THAT HEALTH CARE HAS BECOME TOO IMPERSONAL, DOC.
NONSENSE... JUST RELAX AND LIE BACK ON THE BAR CODE SCANNER.
Rob Rogers / Pittsburgh Post-Gazette

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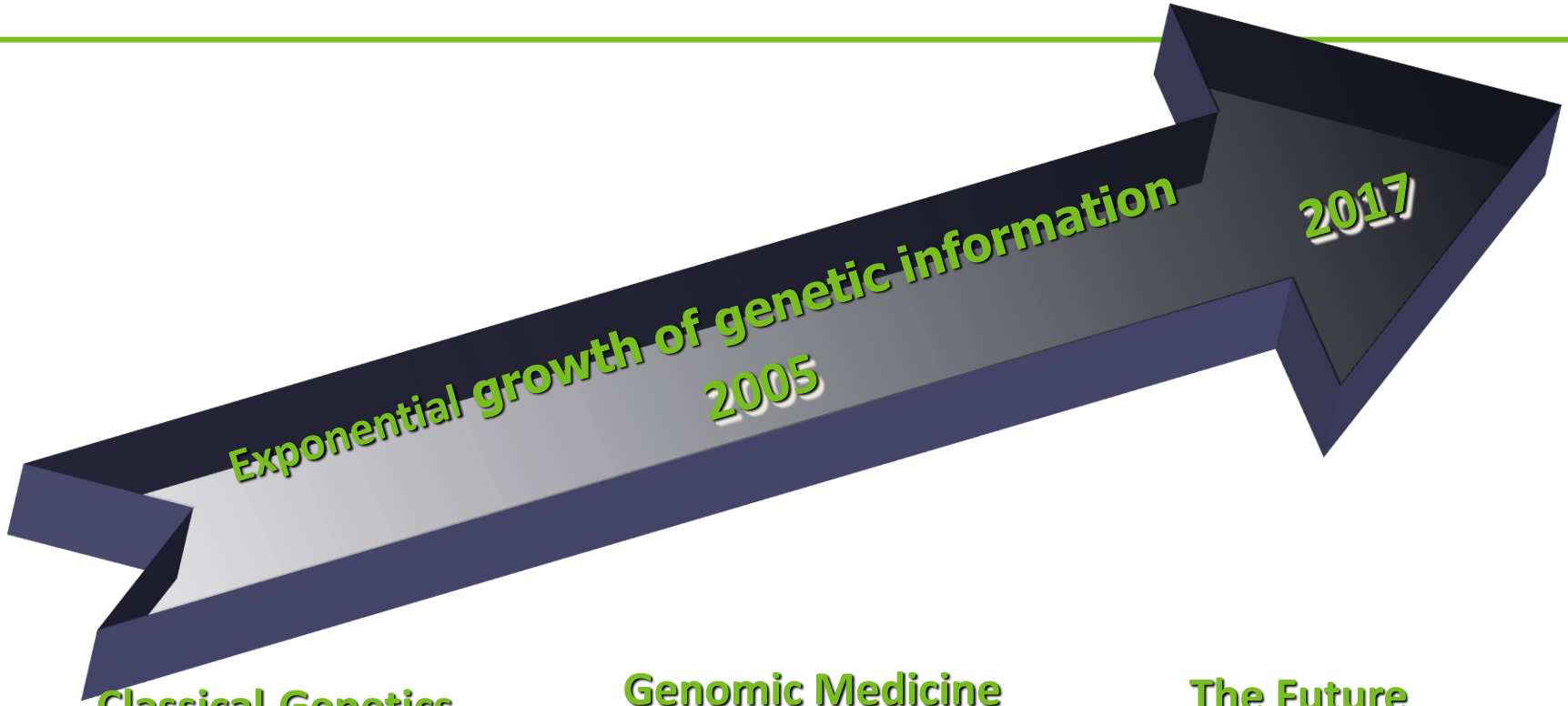
The Evolution of Genetics and Medicine



Classical Genetics

- Defining genetic disorders
- Developing genetic diagnostic tools
- Genetic counselling

Genomic Medicine

- Improving diagnostic capabilities
- Treatment of genetic disorders
- Genomic Counselling

The Future

- Predicting & managing risk
- Disease prevention
- Personalized Medicine

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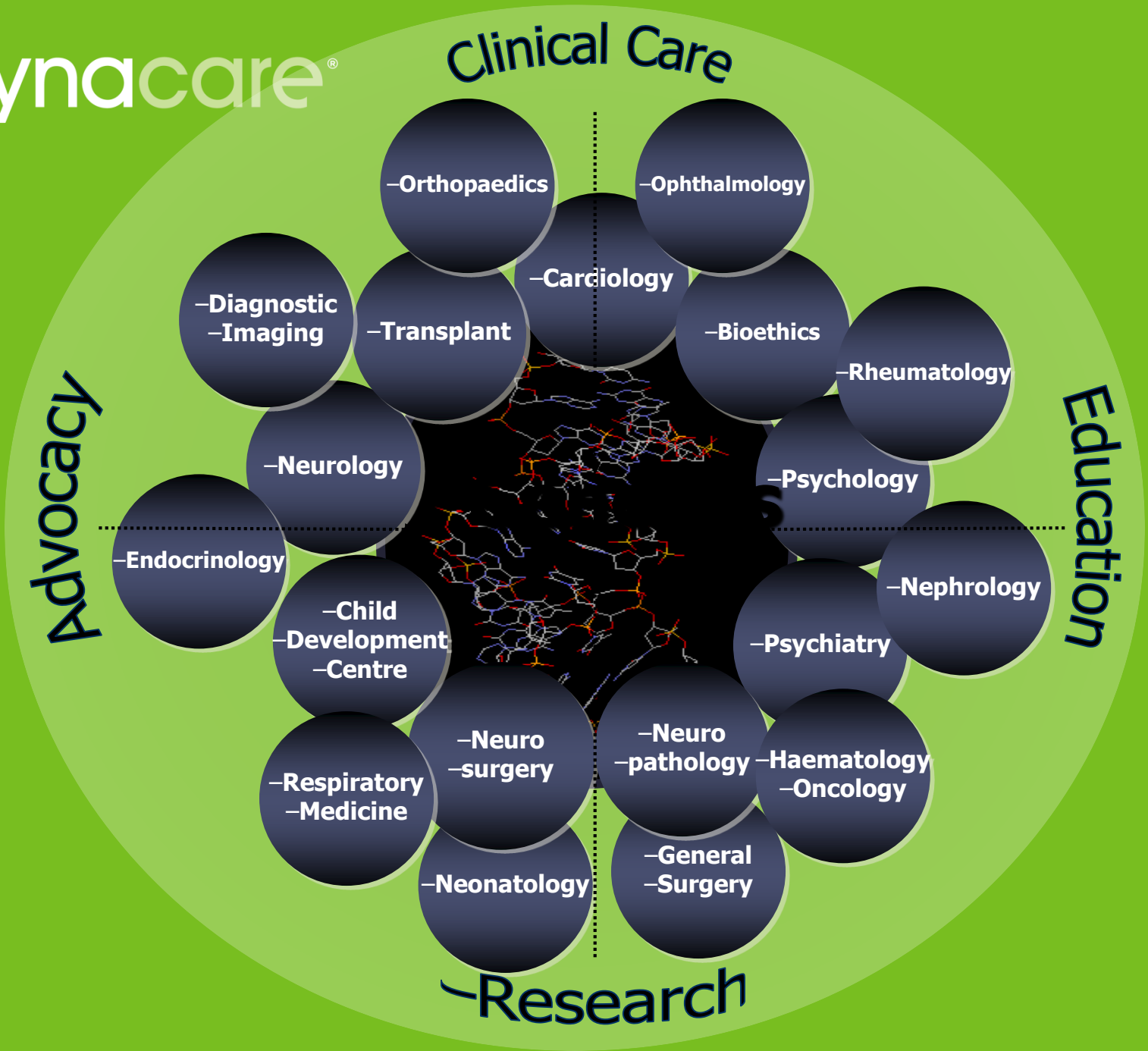
Clinical Care
Education
Research
Advocacy
–Orthopaedics
–Ophthalmology
–Cardiology
–Diagnostic –Imaging
–Transplant
–Bioethics
–Rheumatology
–Neurology
–Psychology
–Endocrinology
–Nephrology
–Child –Development –Centre
–Psychiatry
–Neuro –surgery
–Neuro –pathology
–Haematology –Oncology
–Respiratory –Medicine
–General –Surgery
–Neonatology


Egypt Divided / Pot's Big Moment / Best of 2012
TIME
Want to Know My Future?
Asthma
Diabetes
Cancer
Breast cancer
Tay-Sachs disease
Parkinson's
Obesity
New genetic tests can point to risks—but not always a cure
BY BONNIE ROCHMAN

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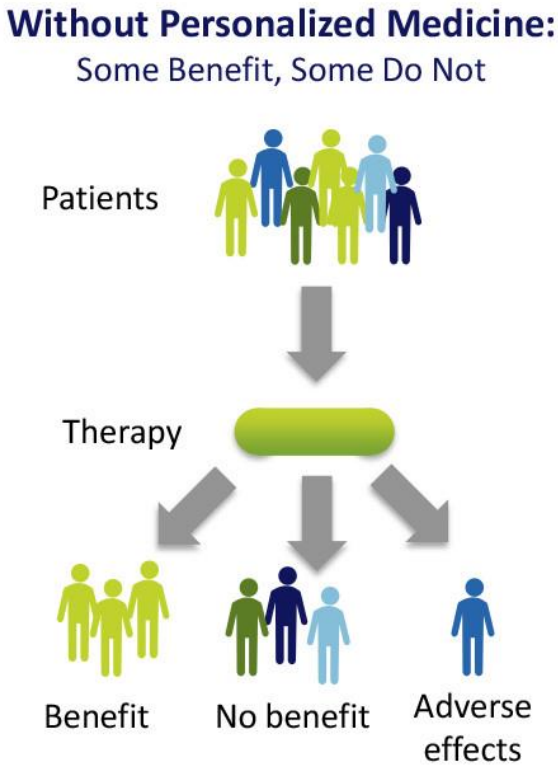
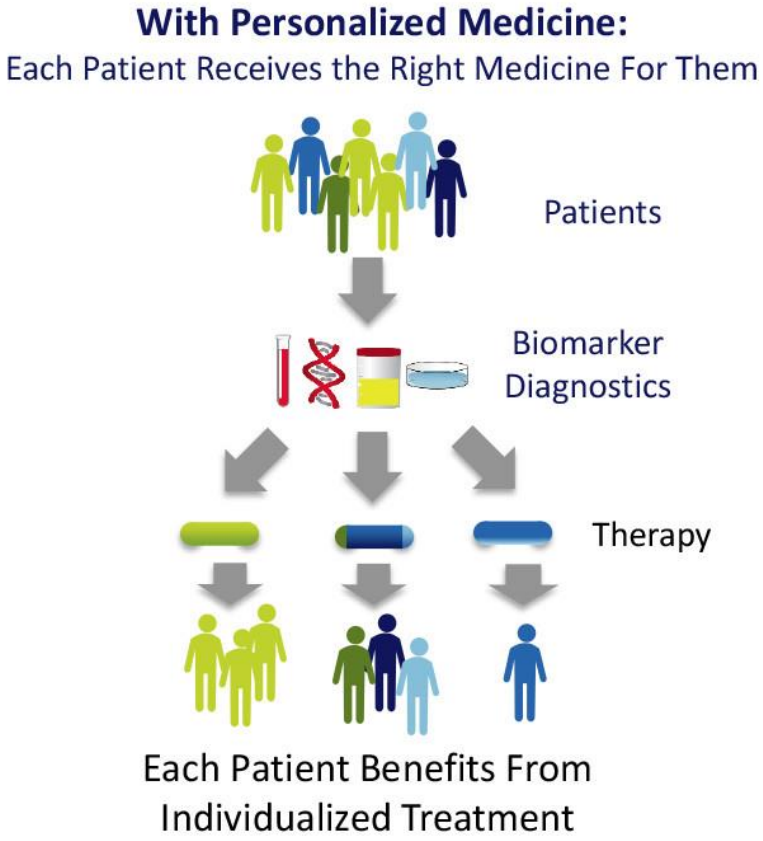
Pharmacogenomics

Clinical Goals

- Avoid adverse drug reactions
- Maximize drug efficacy
- Select responsive patients

Promise of Pharmacogenomics





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Factors Impacting Drug Response

- Age
- Sex
- Diet
- Disease
- Stress
- Pregnancy
- Exercise
- Alcohol Intake
- GI Function
- Renal Function
- Hepatic Function
- CV Function
- Dietary Supplements
- Drug Formulation
- Drug Adherence
- Route of Drug Administration
- Drug-Drug Interactions
- Drug-Food Interactions
- **Drug-Gene Interactions**

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Real Life Concerns

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Why?

- **Adverse Drug Reactions (ADR):**
  - Annually in USA:
    - > 2 million severe ADRs
    - Causes 100,000-218,000 deaths
    - 4th leading cause of death. Thought to be similar in Canada.
    - Estimated to account for up to 30% of hospital admissions in the USA and Canada.
- **Benefits of Pharmacogenomics:**
  - Conservative estimates with rate of test uptake and ADR reductions at 5-10% over 5 years translate to healthcare savings of $6–25M in Canada
  - Improve morbidity and mortality

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Current Recommendations

- **USA:**
  - FDA has included pharmacogenomic information on drug labels for 135 drugs

- **Canada:**
  - Health Canada Drug Product Database –
    - 35 drugs PGx testing required
    - 3 drugs PGx testing recommended
    - >80 drugs w actionable or informative PGx
  - https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
  - https://www.pharmgkb.org/

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Right 10K study

- **Collaboration between Mayo and Baylor**
  - Sequence "Pharmacogenes" for 10k patients
  - Place data pre-emptively in EMR
  - Systematic evaluation of outcomes
- **Main focus**
  - **Retrospective studies:** using EMR to determine adverse drug reactions and lack of efficacy that might have been avoided if pharmacogenetic info had been available
  - **Prospective studies:** of adverse drug reactions and lack of efficacy that were avoided by pre-emptive alerts
  - **Cost Analysis:** of both adverse drug reactions and lack of efficacy
  - **VUS Identification:** and functional study

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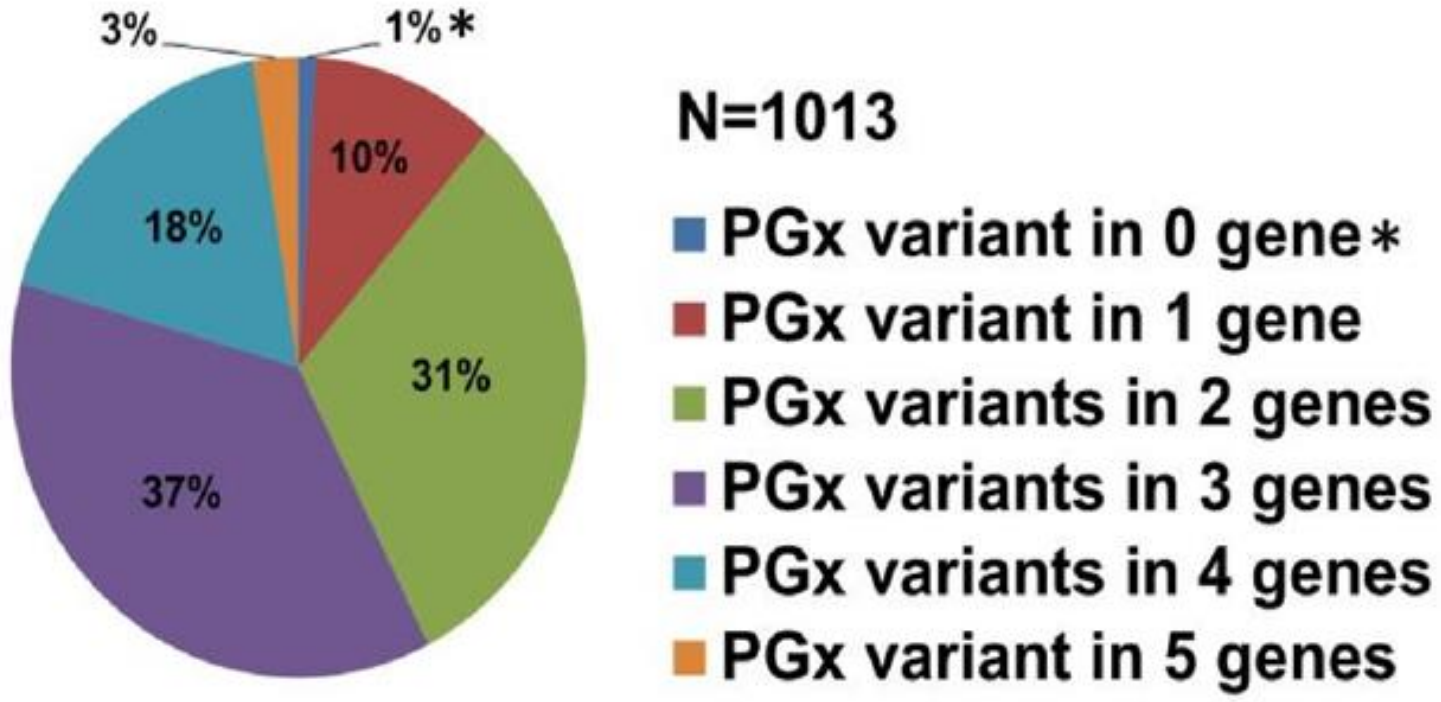
RIGHT Project: Mayo-Baylor Collaboration



Most (99%)patients have PGx variants that affect drug metabolism

Drs. Yuan Ji and John Black, et al. – J. Mol. Diagnostics, 2016

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Project Title: Integrating Pediatric Pharmacogenomic Testing into the Canadian Health Care System

- Partnership with Canadian Pharmacogenomics Network for Drug Safety (CPNDS) at UBC
- $3 Million Genome Canada Grant
- Objectives:
  - Ensure the validity, utility, accuracy and clinical relevance
  - Focused on the three most frequently prescribed therapeutic classes of drugs in children:
    1) antibiotics,
    2) analgesics,
    3) mental health medications

UBC partnership funded to set up pharmacogenomics in 10 hospitals across Canada – partnered with Dynacare

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Patient Results

GENOMIND www.genomind.com

RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) S/S [High risk of non-response]	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs; potential increased risk for PTSD and reduced stress resilience • Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate		**Use caution** with SSRIs **Therapeutic options: atypical antidepressants** or **SNRIs** may be used if clinically indicated
Calcium Channel (CACNA1C) A/A [Highest risk of altered neuronal signaling]	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or lability		**Therapeutic options: atypical antipsychotics, mood stabilizers** and/or **omega-3 fatty acids** may be used if clinically indicated
Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk]	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics **High risk**: Clozapine; Olanzapine; **Medium risk**: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone **Lower risk**: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone		**Use caution** with atypical antipsychotics
Methylenetetrahydro-folate Reductase (MTHFR) C677T: T/T A1298C: A/C [Low activity]	*MTHFR is an enzyme responsible for the conversion of folic acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder		Higher intake of folic acid based interventions may be required **Therapeutic options: l-methylfolate** may be used if clinically indicated
Brain-derived Neurotrophic Factor (BDNF) Met/Met	*BDNF is a protein involved in neuronal development and neural plasticity* • Potential risk for increased depression symptoms, impaired working memory, and altered stress response • Studies have shown that Met carriers may have less satisfactory response to SSRIs in Caucasians, but not Asians, however larger studies need to be conducted to confirm these findings • Exercise has been linked to improvements in cognition, and recent studies show that Met allele carriers may demonstrate enhanced effects of exercise on working memory compared to Val/Val patients		**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate

Interpretation

Drug Interaction Summary:

This summary provides a listing of implications for psychotropic and pain medications specific to your patient's genetic profile

	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: CYP450: Serum levels may be ↑ [reduced dose may be required]	Use with Caution: CYP450: Serum levels may be ↓ [increased dose may be required]	Use with Caution: Increased risk for adverse events or poor response
	Antidepressants			SLC6A4			SLC6A4
SSRIs	Citalopram (Celexa®)	2C19, 3A4/5			✓		✓
SSRIs	Escitalopram (Lexapro®)	2C19, 2D6			✓		✓
SSRIs	Fluoxetine (Prozac®)	2D6, 2C9					✓
SSRIs	Fluvoxamine (Luvox®)	2D6, 1A2					✓
SSRIs	Paroxetine (Paxil®)	2D6					✓
SSRIs	Sertraline (Zoloft®)	--					✓
SNRIs	Desvenlafaxine (Pristiq®)	--	✓	✓			
SNRIs	Duloxetine (Cymbalta®)	1A2, 2D6	✓	✓			
SNRIs	Levomilnacipran (Fetzima®)	3A4/5	✓	✓			
SNRIs	Venlafaxine (Effexor®) [1]	2D6, 2C19		✓	Indeterminate [2]		
Atypicals	Bupropion (Wellbutrin®)	2B6		✓	✓		
Atypicals	Mirtazapine (Remeron®)	2D6, 3A4/5, 1A2	✓	✓			
Atypicals	Trazodone (Desyrel®, Oleptro®)	3A4/5	✓	✓			
Atypicals	Vilazodone (Viibryd®)	3A4/5	✓	✓			
Atypicals	Vortioxetine (Brintellix®)	2D6	✓	✓			

[1] Prodrug - requiring activation by the liver; 2D6 IMs/PMs may experience lower efficacy and increased side effects due to reduced conversion to the active metabolite and higher levels of the inactive parent drug; 2D6 UMs may experience increased conversion of the parent drug, and higher levels of the active metabolite

[2] Indeterminate - Gene-drug interaction may exist, however indeterminate due to varied impact of multiple CYP450 enzymes, unknown clinical significance of a rare variation, or genotype was unable to be determined.

Aetna Health Insurance - Mental Health & Pharmacogenetics Study

A retrospective propensity-score matched case-control analysis[1] demonstrated the impact of the Genecept Assay on utilization and cost of care in a large commercial health plan

(n = 817 Genecept-tested patients, and 2,745 matched controls)

Patients tested with Genecept have **lower total costs** than untested patients

Genecept saves an average of $3,897 per patient per year in total costs

– Annualized cost savings*

–In a health plan with 1,000 mood disorder patients, Genecept-guided treatment could result in **cost savings of ~$3.9 million per year**

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Cancer is common

- Canadian Cancer Statistics 2016 (www..cancer.ca)

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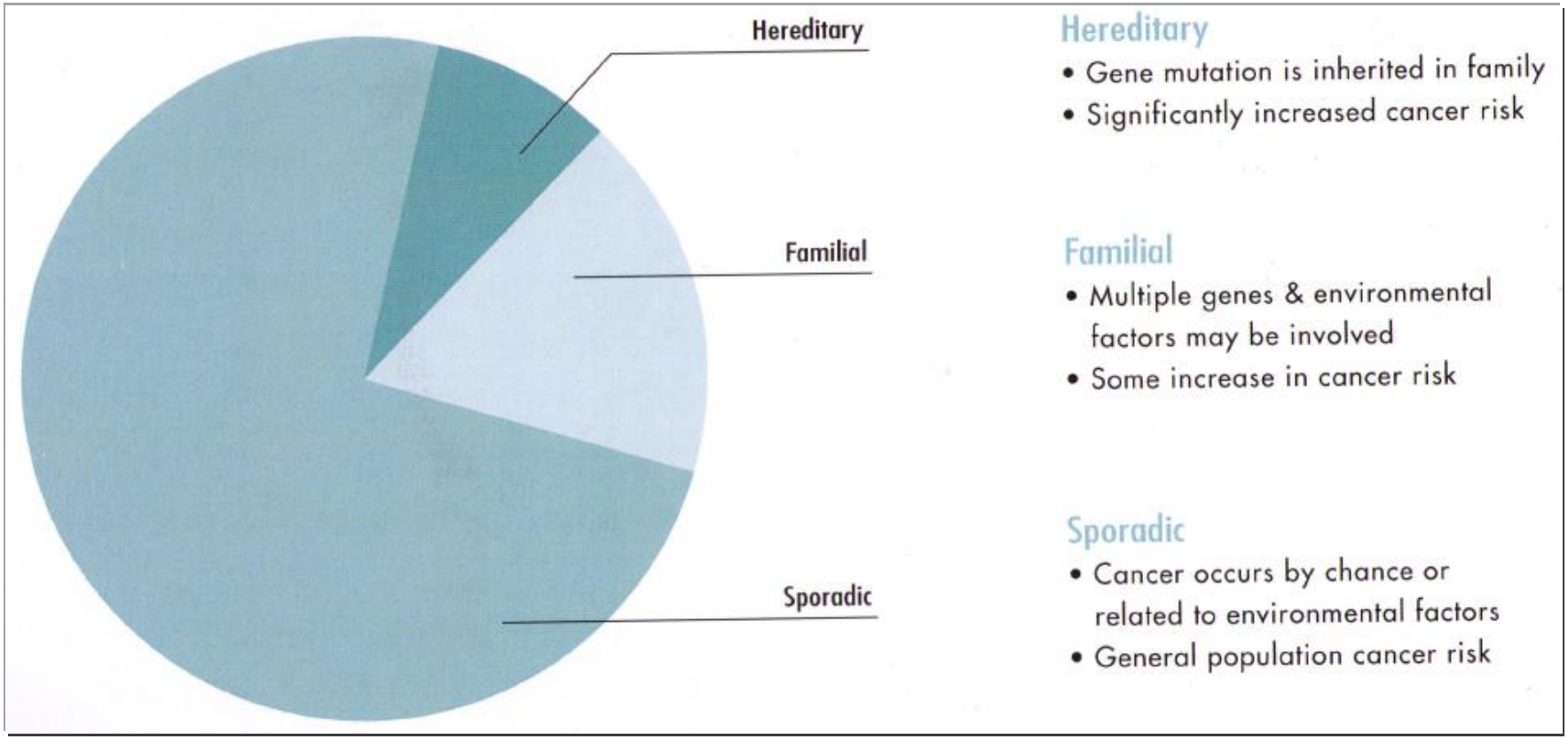
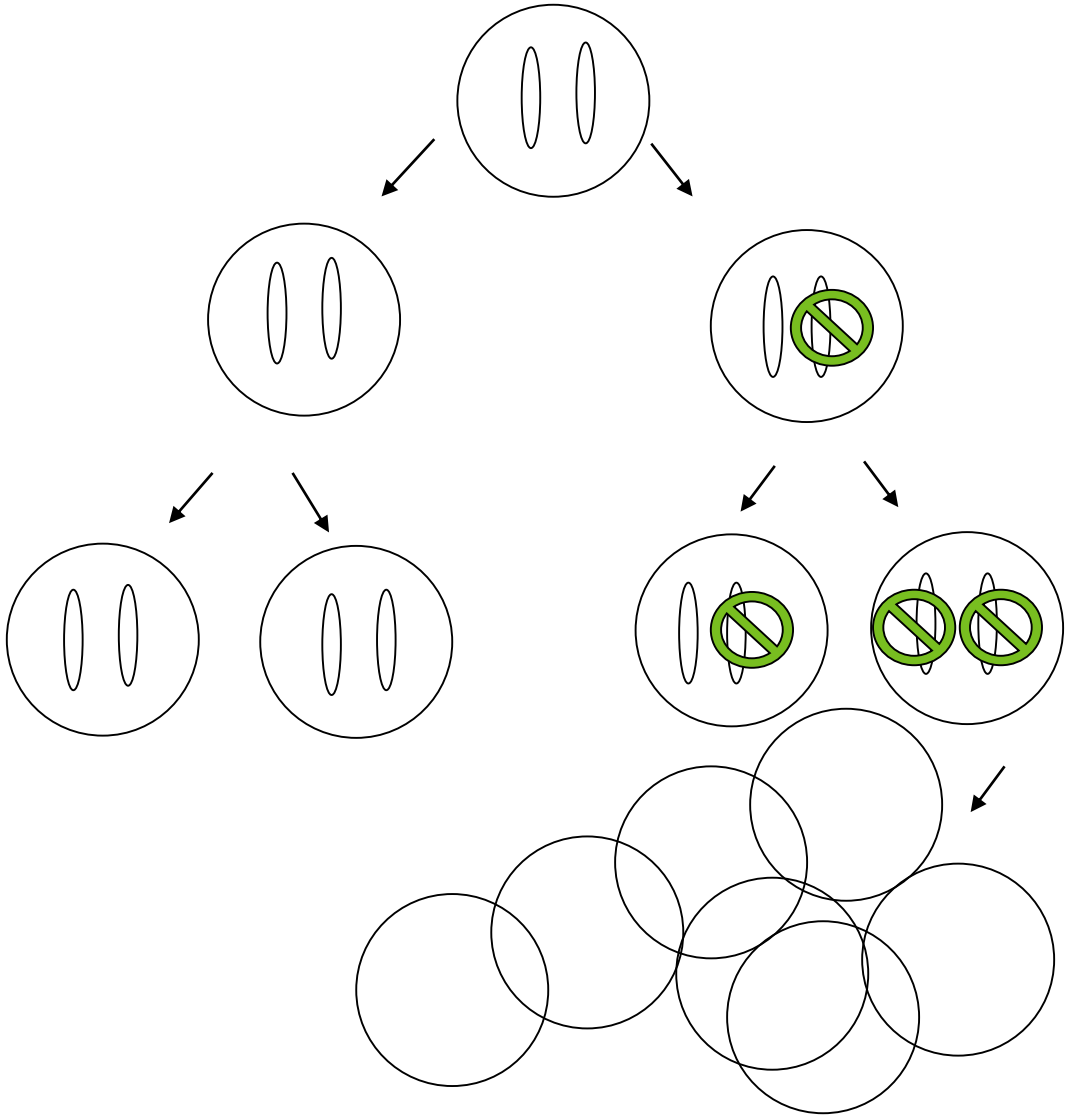
Cancer in Families

All cancer is genetic, but not all cancer is heritable



What is Cancer? - Sporadic Type



–First mutation
–(Acquired)

–Second mutation
–(Acquired)

–Cancer

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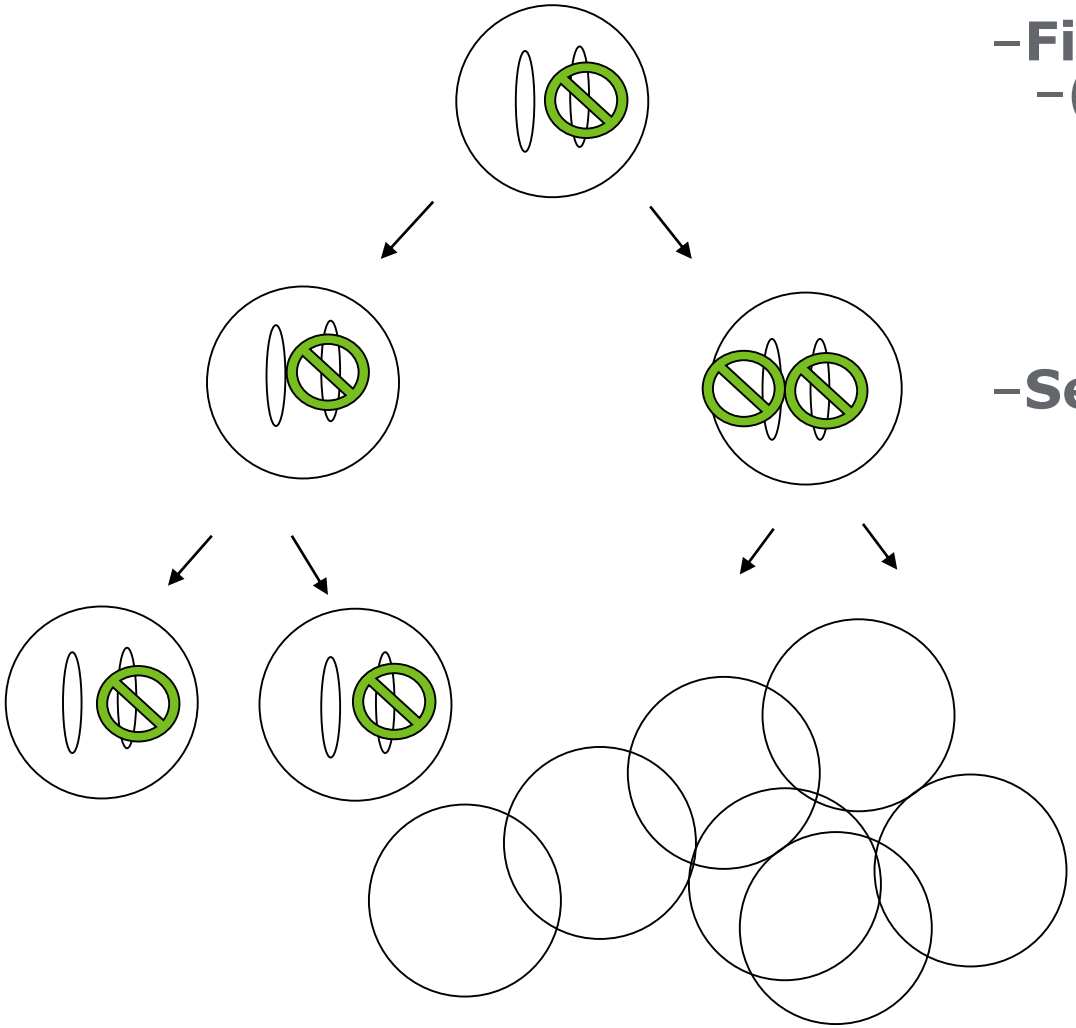
What is Cancer? - Hereditary Cancer



–First mutation
–(Inherited)

–Second mutation
–(Acquired)

–Cancer

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Cancer Pharmacogenomics

- **Two Genomes**
  - Germline Genome
  - Tumour Somatic Genome

Germline-Somatic Genome PGx Cross-Talk

- **Mainstream Pharmacogenetics**
  - EGFR
  - KRAS

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What to watch for in the future…

- Decreased cost
  - More patients tested
  - More genes/variants included in tests
- Transition from genotyping ⇒ sequencing
  - More rare variants identified
- Increasing knowledge about interactions amongst multiple variables ⇒ increasing complexity
  - Genes, medications, supplements, environment, patient's overall health/comorbidities

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Thank You
Questions?