From Genes to Medications: Transforming Patient Outcomes Through Pharmacy-Genetic Counseling Partnerships

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Financial Disclosures- Jordan Brady

I have no relevant financial disclosures.

Financial Disclosures – Josiah Allen

I currently have or have had the following relevant financial relationships during the past 24 months:

- Nurture Genomics Consultant – Current
- Precision Genetics Consultant – Past

Learning objectives

Describe the overlap between hereditary genetic conditions and medication prescribing

Propose an approach for including pharmacy services in clinical genomic care.

Agenda

01

Discuss the ways in which genetics professionals may utilize pharmacy services

02

Discuss the ways in which pharmacy professionals may utilize genetics services

03

Case examples

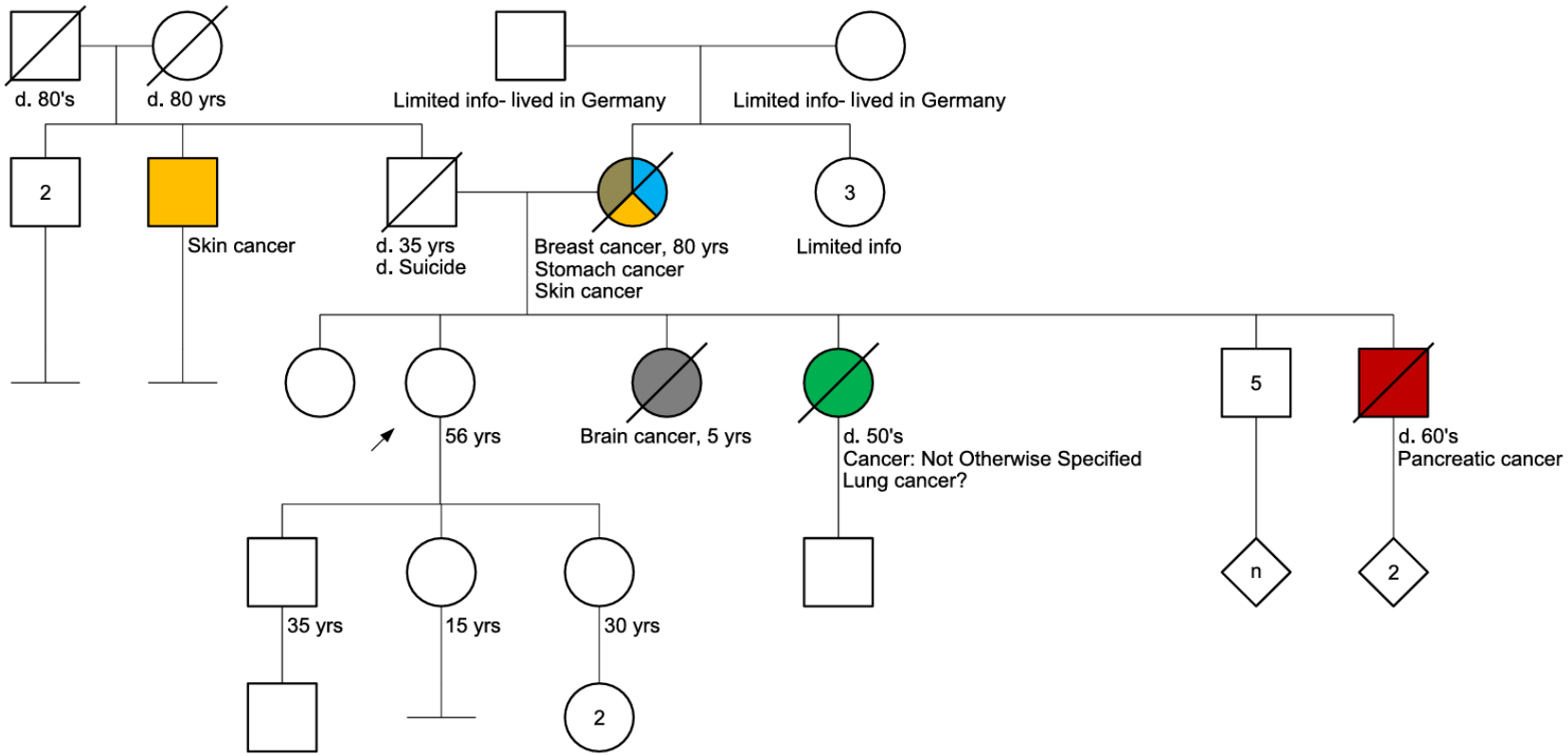
04

Discuss approaches to integrated pharmacy and genomic care

Case Example 1

Case: Seeing RET

- 54 y.o. female who presented to the genetic counseling clinic to discuss her family history of cancer.
- Problem list:
  - CKD
  - Atrial fibrillation
  - Diabetes mellitus, type II
  - Pulmonary hypertension



Case: seeing RET

- Positive finding is indicative of multiple endocrine neoplasia type 2 (MEN2)
- Concern for medullary thyroid cancer, pheochromocytoma and parathyroid adenoma
- Seen in cancer prevention clinic to discuss risk for thyroid cancer as well as breast/ovarian cancers

RESULT: POSITIVE

One Pathogenic variant identified in PALB2. PALB2 is associated with autosomal dominant hereditary breast and pancreatic cancer and autosomal recessive Fanconi anemia.

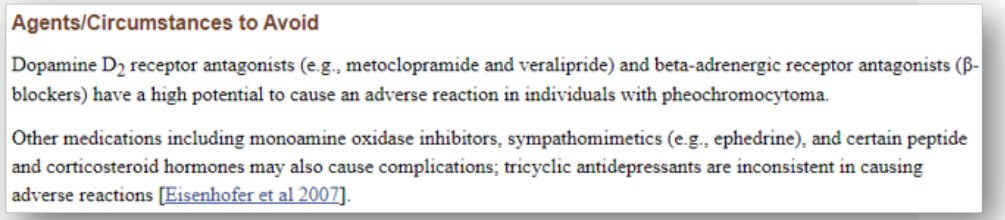
One Pathogenic variant identified in RET. RET is associated with autosomal dominant multiple endocrine neoplasia and nonsyndromic Hirschsprung disease.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PALB2	c.2470dup (p.Cys824Leufs*2)	heterozygous	PATHOGENIC
RET	c.1826G>A (p.Cys609Tyr)	heterozygous	PATHOGENIC

About this test

This diagnostic test evaluates 75 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

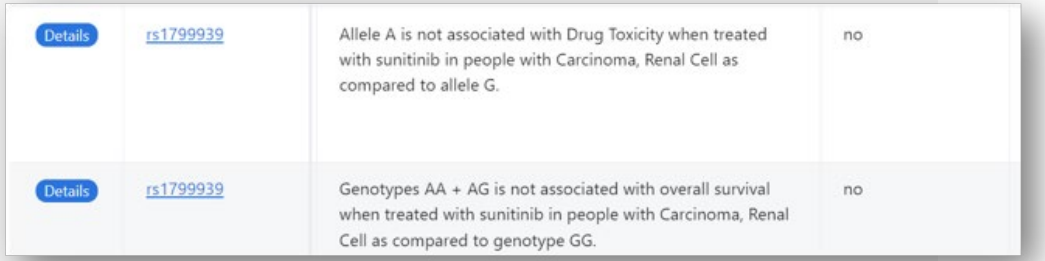
Case: Seeing RET



Agents/Circumstances to Avoid

Dopamine D_2 receptor antagonists (e.g., metoclopramide and veralipride) and beta-adrenergic receptor antagonists (β-blockers) have a high potential to cause an adverse reaction in individuals with pheochromocytoma.

Other medications including monoamine oxidase inhibitors, sympathomimetics (e.g., ephedrine), and certain peptide and corticosteroid hormones may also cause complications; tricyclic antidepressants are inconsistent in causing adverse reactions [Eisenhofer et al 2007].



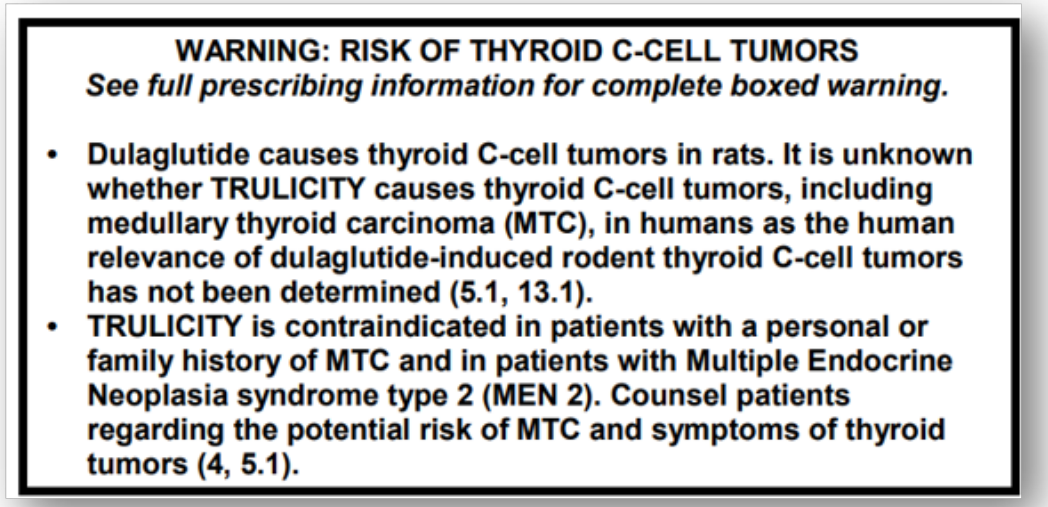
Details	rs1799939	Allele A is not associated with Drug Toxicity when treated with sunitinib in people with Carcinoma, Renal Cell as compared to allele G.	no
Details	rs1799939	Genotypes AA + AG is not associated with overall survival when treated with sunitinib in people with Carcinoma, Renal Cell as compared to genotype GG.	no

- Review of common resources
  - **PharmGKB:** Included label information on mutations in *RET* in somatic tumor samples
  - **CPIC:** No mention
  - **Genereviews:** Increased risk of adverse events with D2 antagonists and beta blockers in patients with pheochromocytoma.
    - Patient was on a beta blocker but is not diagnosed currently with a pheochromocytoma.

Case Closed?

Case: Seeing RET

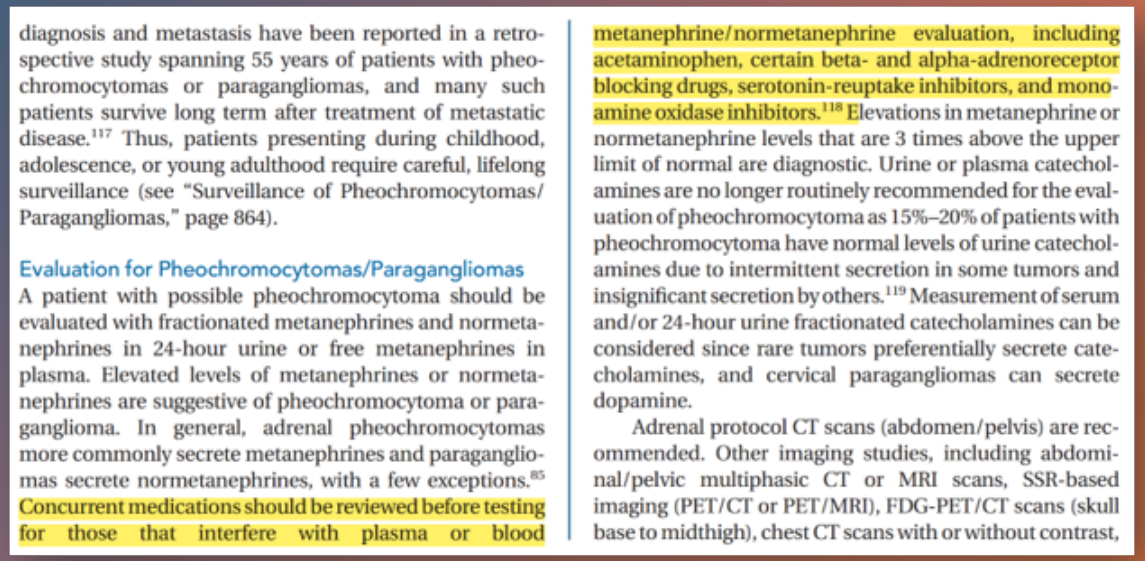
- A diagnosis of MEN2 is a contraindication for GLP-1 agonists, FDA “black box” warning
- Patient was taking Trulicity for her DM, type II, greatly increasing her risk of thyroid cancer
- Trulicity was discontinued and an SGLT2 inhibitor was started



WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**



diagnosis and metastasis have been reported in a retrospective study spanning 55 years of patients with pheochromocytomas or paragangliomas, and many such patients survive long term after treatment of metastatic disease.[117] Thus, patients presenting during childhood, adolescence, or young adulthood require careful, lifelong surveillance (see "Surveillance of Pheochromocytomas/Paragangliomas," page 864).

Evaluation for Pheochromocytomas/Paragangliomas

A patient with possible pheochromocytoma should be evaluated with fractionated metanephrines and normetanephrines in 24-hour urine or free metanephrines in plasma. Elevated levels of metanephrines or normetanephrines are suggestive of pheochromocytoma or paraganglioma. In general, adrenal pheochromocytomas more commonly secrete metanephrines and paragangliomas secrete normetanephrines, with a few exceptions.[85] Concurrent medications should be reviewed before testing for those that interfere with plasma or blood metanephrine/normetanephrine evaluation, including acetaminophen, certain beta- and alpha-adrenoreceptor blocking drugs, serotonin-reuptake inhibitors, and monoamine oxidase inhibitors.[118] Elevations in metanephrine or normetanephrine levels that are 3 times above the upper limit of normal are diagnostic. Urine or plasma catecholamines are no longer routinely recommended for the evaluation of pheochromocytoma as 15%–20% of patients with pheochromocytoma have normal levels of urine catecholamines due to intermittent secretion in some tumors and insignificant secretion by others.[119] Measurement of serum and/or 24-hour urine fractionated catecholamines can be considered since rare tumors preferentially secrete catecholamines, and cervical paragangliomas can secrete dopamine.

Adrenal protocol CT scans (abdomen/pelvis) are recommended. Other imaging studies, including abdominal/pelvic multiphasic CT or MRI scans, SSR-based imaging (PET/CT or PET/MRI), FDG-PET/CT scans (skull base to midthigh), chest CT scans with or without contrast,

Case: Seeing RET

- Subsequent research also identified another interaction:
  - Metanephrine levels are used to screen for pheochromocytoma per NCCN guidelines
  - Acetaminophen, alpha and beta adrenergic blockers, SSRIs and MAOIs can falsely elevate metanephrine levels, leading to false positives
  - Patient was taking acetaminophen and metoprolol which would interfere with her screening

How Genetics Professionals and Pharmacy Professionals Can Work Together

Genetic Counseling Scope of Practice

Genetic counselors (GCs) are trained in genetics expertise, psychosocial counseling, education and professional development.

GCs are NOT able to make management recommendations including: ordering imaging or lab work, prescribing medications or treatments, etc.

In general, GCs are not trained to consider the pharmacological impactions of genetic conditions.

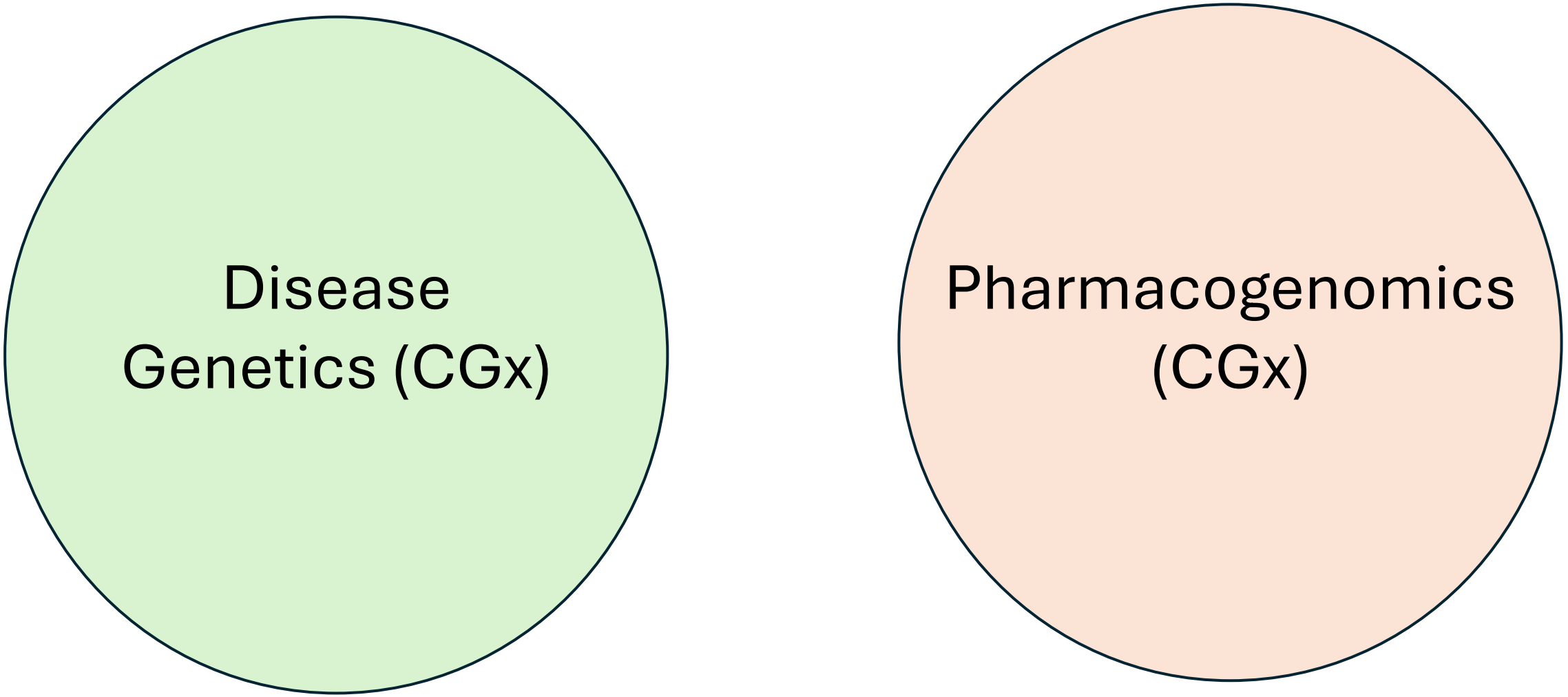
PGx Pharmacist Scope of Practice

Pharmacists are trained in clinical pharmacology and pharmacotherapy. PGx pharmacists have advanced training in the genetics of medication response.

However, pharmacists (including PGx pharmacists) are NOT trained in clinical genetics and receive very little training on genetic disorders.

Pharmacists may not diagnose but can make pharmacotherapy and lifestyle recommendations. Pharmacists may prescribe medications under a collaborative agreement with a prescriber.

Areas of Genomics



Types of Genetics Professionals

- Survey of 3,070 genetics professionals in the US:
  - 66.0% Genetic Counselors
  - 15.4% Clinical Geneticists
  - 12.2% Laboratory Geneticists
  - 4.7% Metabolic dieticians
  - 1.7% genetic nurses or Pas

P499: US genetics professional workforce in 2023 - ScienceDirect

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Professionals in RED either do not prescribe medications as part of their role or are not able to/trained to.

How genetics professionals can utilize pharmacy

Consideration/involvement in patient management and follow up when a genetic result is identified	Requesting pharmacy review of genetic results for pharmacotherapy implications
Development of tailored treatment plans	Communicating with providers about medications that may be indicated or contraindicated
Identification and referral of patients who may benefit from PGx testing	e.g. a patient undergoing genetic testing for familial hypercholesterolemia with statin intolerance

How pharmacy can utilize genetics professionals

Identify Patients Who Qualify for Clinical Genomic Testing (CGx)

e.g. Identification of a patient who had PGX testing for a statin and qualifies for hereditary familial hypercholesterolemia testing

Opportunities for both genetics and pharmacy in patient cases

Malignant hyperthermia: GC can discuss inheritance/limitations of genetic testing; PharmD can discuss medication implications

Factor V: PharmD can educate patients/providers on when anticoagulant therapy is indicated; GC can provide more in-depth counseling on genetic inheritance and family planning options.

Precision Medicine Centered Care

e.g. Involving genetics professionals in lit review/case discussions involving patients with inherited genetic conditions

Question

Which of these conditions has a pharmacological implication to consider:

A) Marfan syndrome

B) Myotonic dystrophy

C) Multiple endocrine neoplasia type 2

D) All of the above

Check-In Question

Which of these conditions has a pharmacological implication to consider:

A) Marfan syndrome – Fluoroquinolone antibiotics, decongestants, triptans

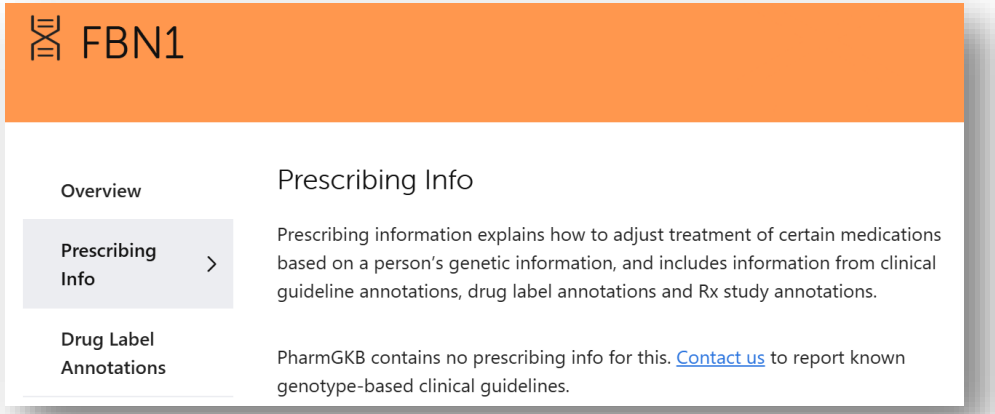
B) Myotonic dystrophy –anesthesia risk

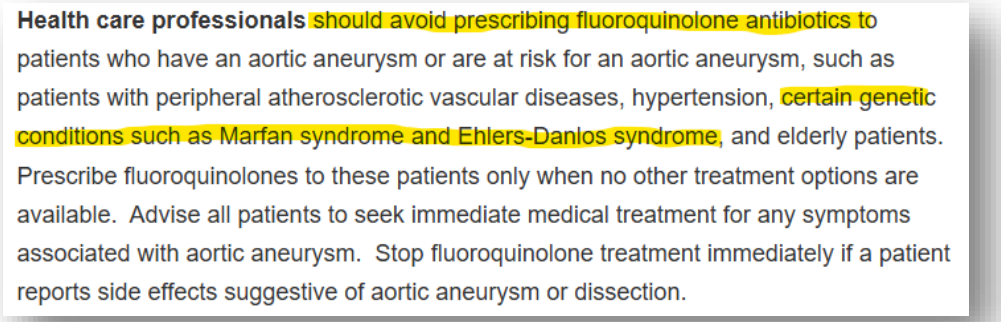
C) Multiple endocrine neoplasia type 2 – GLP-1 agonists

D) All of the above

Case Example 2

Case 2: Marfan Syndrome





- Marfan syndrome is a connective tissue disorder caused by variants in *FBN1*.
- Primary morbidity/mortality concern is aortic dissection.
- In Dec 2018, the FDA released a safety communication warning of increased risk of aortic dissections with fluoroquinolone antibiotics.
- This concern is not mentioned in online resources such as PharmGKB.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics

How often do these interactions present?

Preliminary Research

- Focused on the ACMG Secondary Findings 3.2 list
- From ACMG, the list provides "recommendations for a minimum list of gene-phenotype pairs for opportunistic screening to facilitate the identification and/or management of risks for selected genetic disorders through established interventions aimed at prevention or significantly reducing mortality"
- In short, a curated list of genes that are high evidence and interventions can be taken to reduce morbidity and mortality
- 81 genes on version 3.2 (97 genotype-phenotype pairs)

Methods

- Two pharmacogenomic pharmacists and one genetic counselor reviewed each gene and provided a specific "level" of interaction

Level 1	Level 2A	Level 2B	Level 3
CPIC, DPWG, or FDA recommendations medication therapy adjustment.	Exposure to drug can contribute to the risk disease emergence	Exposure to drug can exacerbate genetic disease symptoms	No interaction or very weak association reported

Resources Utilized in this Study

- International point-of-care resource providing clinically relevant and medically actionable information on inherited conditions
- Currently has 910 chapters
- Typically contains an “agents/circumstances to avoid” section

Publicly available database of:

- Curation of peer-reviewed PGX literature, drug labels, and prescribing guidelines
- Standardized annotations assess variant-drug phenotype association

- Assess clinical validity and actionability of genes and their relationship to diseases
- Encourage data sharing
- Expertly curating and interpreting variants

- Federal agency that regulated various products related to health and safety
- Provides warnings for medications that have serious safety risks

Question Check-In

Of 97 genotype-phenotype pairs on the ACMG SF list, what percentage have a clinically significant medication implication?

A) 5%

B) 15%

C) 25%

D) 35%

E) >50%

Preliminary Results

- Of 97 gene-phenotype pairs reviewed:
  - 22 (23%) level 1
  - 31 (32%) level 2
  - 44 (42%) level 3

Answer: Over half (55%) of gene-phenotype pairs were a level 1 or level 2 interaction, or had a significant medication implication

Results: Level 1 (n = 22 gene-phenotype pairs)

Gene	Condition	Affected Medications
ATP7B	Wilson disease	Copper IUD and supplements, Platinum-containing chemotherapies
CACNA1S, RYR1	Malignant hyperthermia	Inhaled anesthetics, statins
CALM1, CALM2, CALM3, KCNH2, KCNQ1, SCN5A, TRDN	Long QT Syndrome	QT prolonging agents
SCN5A	Brugada syndrome	Lithium, Propafenone, vagotonic agents, alpha-adrenergic agents, beta-adrenergic antagonists, tricyclic antidepressants, first-generation antihistamine, class 1C antiarrhythmics, and class 1A antiarrhythmics
HFE	Hereditary hemochromatosis (c.845G>A; p.C282Y homozygotes only)	Iron supplements, Vitamin C
OTC	Ornithine transcarbamylase deficiency	Valproate, haloperidol, systemic corticosteroids
RET	Familial medullary thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B	GLP-1 agonists, atomoxetine, SSRI, SNRI, beta blockers
MAX, SDHAF2, SDHB, SDHC, SDHD, TMEM127	Hereditary paraganglioma-pheochromocytoma syndrome	Atomoxetine, SSRI, SNRI, beta blockers

Results: Level 2A (n = 15 gene-phenotype pairs)

Gene	Condition	Affected Medications	Rationale
BRCA1, BRCA2, PALB2	Hereditary breast and ovarian cancer	Estrogen-containing contraceptives	May increase breast cancer risk
CALM1, CALM2, CALM3, CASQ2, RYR2, TRDN	Catecholaminergic polymorphic ventricular tachycardia (CPVT)	Digoxin	May increase risk of CPVT episodes
FBN1	Marfan syndrome	Fluoroquinolones, decongestants, vasoconstrictors, triptans	May increase risk of aortic dissection
SMAD3, TGFBR1, TGFBR2	Loeys-Dietz Syndrome	Fluoroquinolones, Decongestants, triptans	May increase risk of aortic dissection
TSC1, TSC2	Tuberous sclerosis complex	Estrogen-containing products	May increase risk of pulmonary lymphangioleiomyomatosis

Results: Level 2B (n = 16 gene-phenotype pairs)

Gene	Condition	Affected Medications	Rationale
ACVRL1, ENG, SMAD4	Hereditary hemorrhagic telangiectasia	Anticoagulants, aspirin, NSAIDs	May increase risk of bleeding
ACTC1, FLNC, MYBPC3, MYH7, MYL3, PRKAG2, TNNI3, TNNT2, TPM1	Hypertrophic cardiomyopathy	Amlodipine, lisinopril, enalapril, digoxin	-Amlodipine, enalapril, and lisinopril may increase risk of symptomatic hypotension in patients with hypertrophic cardiomyopathy -Digoxin can decrease cardiac output
BMPR1A, SMAD4	Juvenile polyposis syndrome	Anticoagulants, aspirin, NSAIDs	May increase risk of bleeding
GAA	Pompe disease	Digoxin, inotropes, diuretics, after-loading agents	- The use of digoxin, inotropes, diuretics, and afterload-reducing agents may worsen left ventricular outflow obstruction, although they may be indicated in later stages of the disease.

Resource Identification

- There was not a singular resource that identified all level 1 and 2 interactions

Clear opportunity for collaboration between clinical genomics and pharmacogenomics professionals!

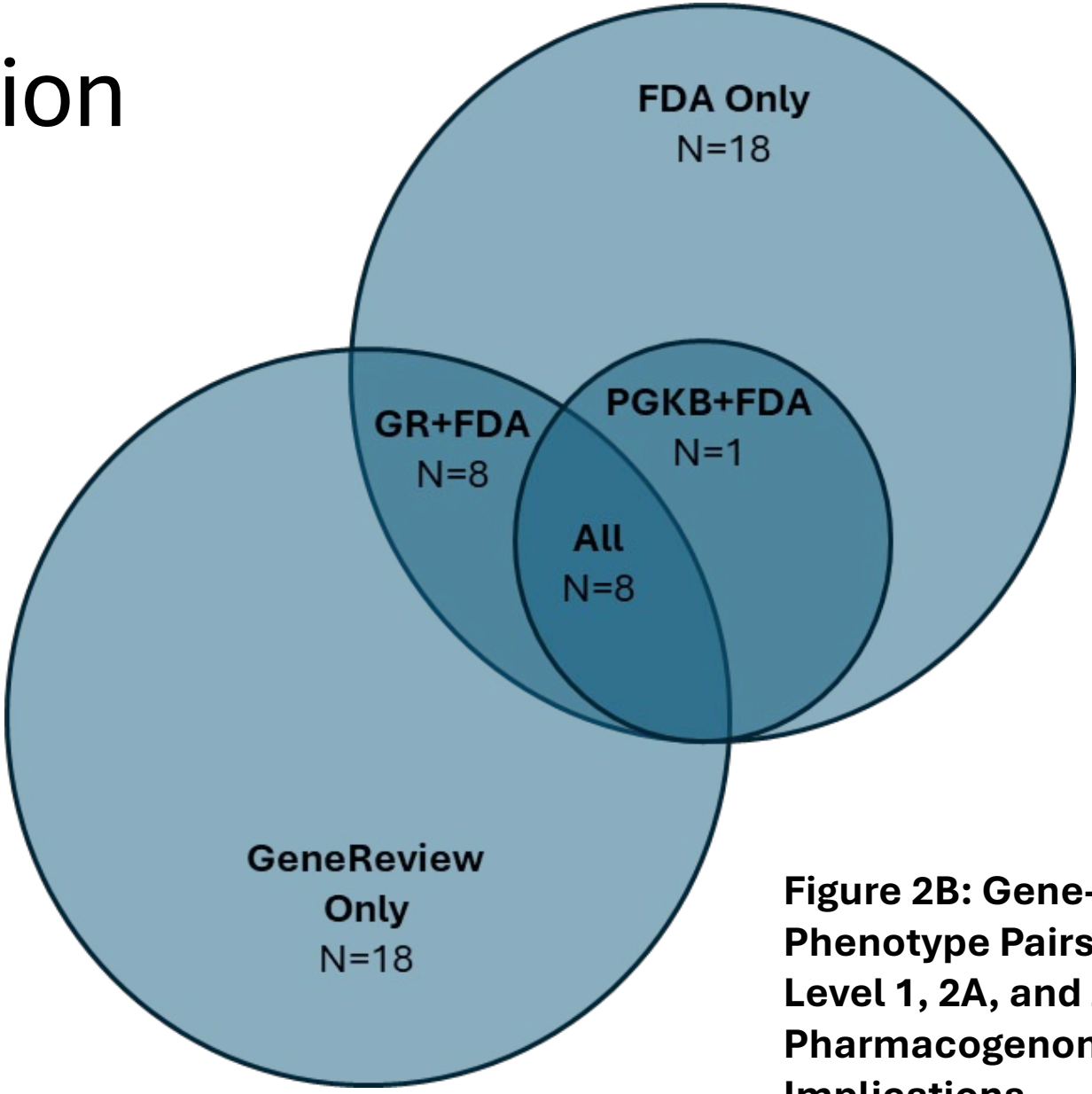


Figure 2B: Gene-Phenotype Pairs with Level 1, 2A, and 2B Pharmacogenomic Implications

How to Integrate Pharmacy and Clinical Genetics

Step 1: Create a Multi-Disciplinary Team

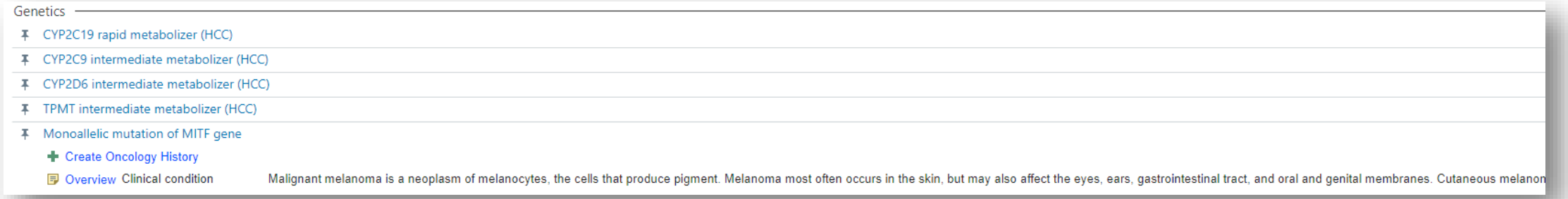
Integrating genetics into pharmacy practice requires strong collaboration with clinical geneticists, genetic counselors, and physicians.

Pharmacists can help interpret pharmacogenetic results, considering drug interactions and overall patient health.

Gene	Condition	Category	Implication
RET	MEN2	Cancer	GLP-1 agonists
SMAD4	Juvenille polyposis	Cancer	Aspirin, NSAIDs, antigoagulants
SDHB, SDHD, SDHC, SDHAF2, TMEM127	Para/Pheo	Cancer	Atomoxetine
FBN1	Marfan Syndrome	Cardio	Fluoroquinolone antibiotics, Decongestants, Triptans
TGFBR2	Loeys-Dietz	Cardio	Fluoroquinolone antibiotics, Decongestants, Triptans
DMPK	Myotonic Dystrophy	Neuro	Anesthesia risk
DMD	DMD/BMD	Other	Anesthesia risk
EMD	Emery-Dreifuss MD	Other	Anesthesia risk
ACVRL1	HHT	Other	anticoagulants, anti-inflammatory agents
ALPL	Hypophosphotasia	Other	Bisphosphonates
CMT	Charcot-Marie Tooth	Neuro	Vincristine, Paclitaxel
SCN5A	Brugada syndrome	Cardio	Avoid QT prolonging drugs
KCNQ1	Long QT	Cardio	Epinephrine, avoid QT prolonging drugs
KCNH2	Long QT	Cardio	HERG-altering drugs like erythromycin, avoid QT prolonging drugs

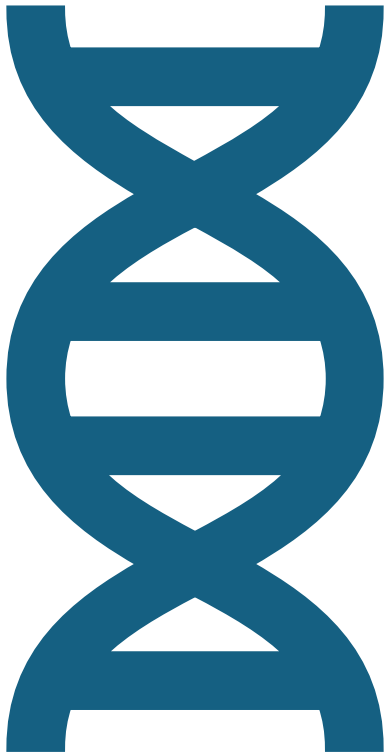
Step 2: Create Visibility

- As you discover these overlapping scenarios, start to create reference guides- not all genetics professionals will think of pharmacy when receiving a positive result
- Use EMR indicators/BPAs flagging a physician when an adverse medication reaction is associated with the patient's diagnosis



Step 2: Create Visibility

- Problem list entries for genetic conditions can trigger incidental review.
- In this patient, PGx testing was ordered to guide antidepressant therapy. Presence of *MITF* gene mutation on problem list triggered more in-depth review.
- *MITF* variants increase risk of cutaneous malignant melanoma. Pharmacist recommended avoiding phototoxic medications (e.g. hydrochlorothiazide) that would further increase risk of melanoma.



Step 3: Provider Education

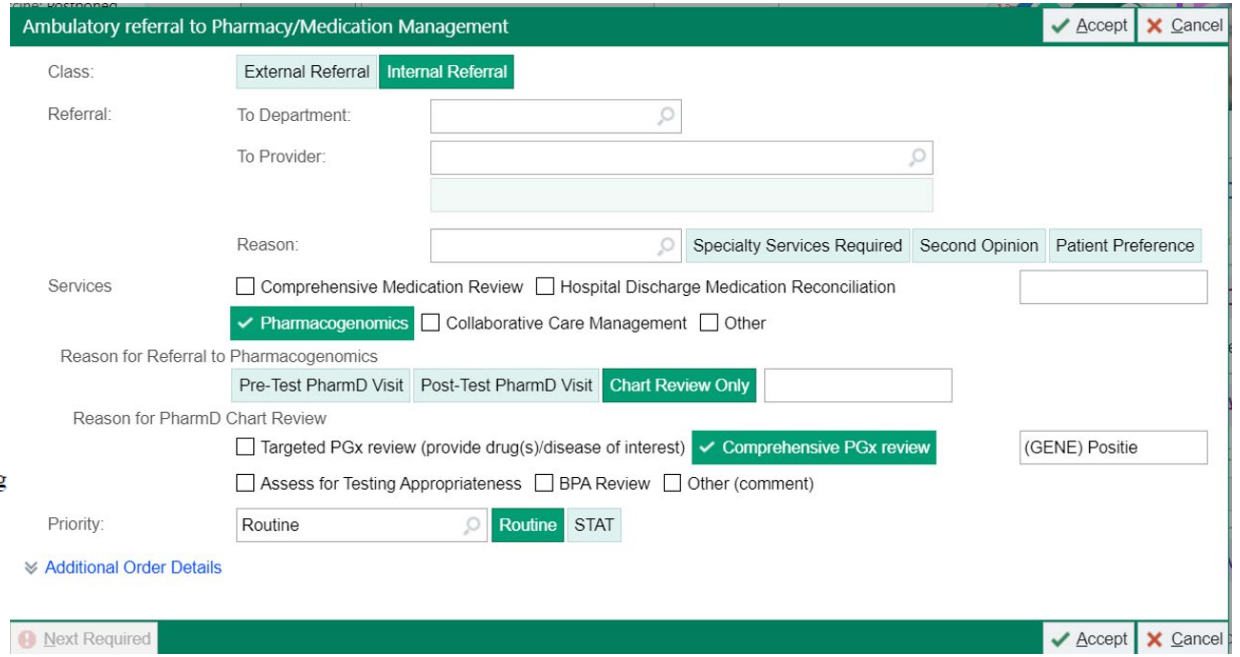
- Encourage both genetics and non-genetics providers to think in a more multi-disciplinary fashion
- Encourage referrals to pharmacogenomic pharmacists if clinical resources mention a possible drug-gene interaction
- Ensure that when a genetic diagnosis is received, that the patient is in the care of providers who are comfortable in the care of patients with this condition and coordination various specialty visits as needed

Our Process At St. Elizabeth

- Patient received a positive result, genetic provider reviews the result and possible implications
- Genetic counselor notices possible interaction while doing a review

Agents/circumstances to avoid: Cholesterol-lowering medications (i.e., statins), which can cause muscle pain and weakness; the anesthetic agent vecuronium; succinylcholine, propofol, and doxorubicin; smoking; obesity; illicit drug use; excessive alcohol intake.

- Genetic Counselor places a referral to pharmacy



Next steps

The pharmacist reviews patient history, interaction and level of evidence available

Will create a note regarding these recommendations and inform relevant providers if any updates are needed to the patients' medications.

Limitation: if resources do not identify a risk, that does NOT mean there is no risk. In the future, pharmacist review may expand to all positive genetic findings.

Looking towards the future

Board of Pharmacy Specialties (BPS) call for pharmacogenomic certification

EMR capabilities should be utilized to help notify providers of potential medication interactions

More systematic reviews of pharmacotherapy implications of genetic conditions are needed!

Questions?