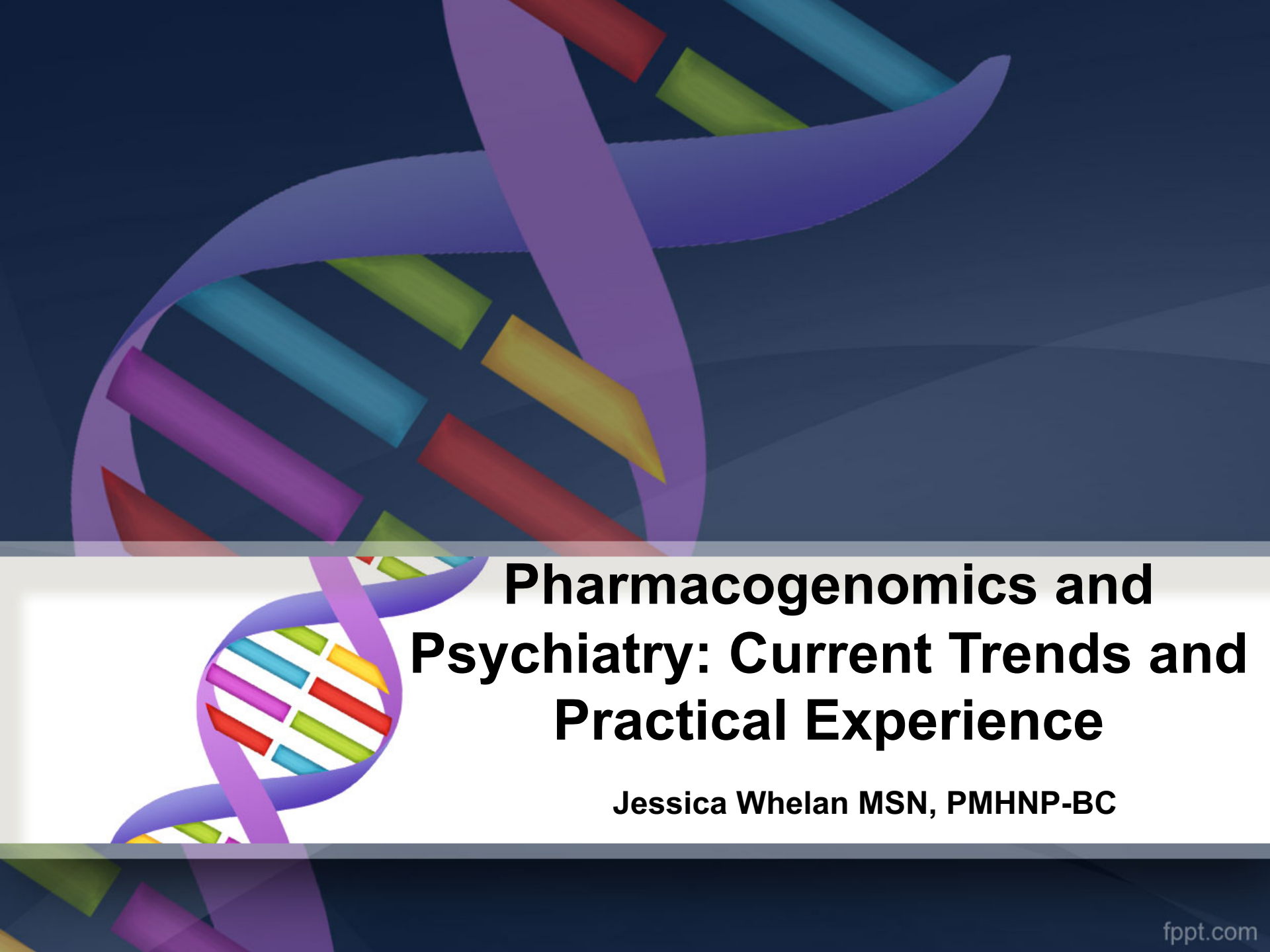


Pharmacogenomics and Psychiatry: Current Trends and Practical Experience

Jessica Whelan MSN, PMHNP-BC

Learning Theory: VARK

- V – visual learning
- A – Auditory Learning
- R – Reading / Writing Learning
- K – Kinesthetic Learning

Estimated Length of Presentation: 90min

Target Audience: Practitioners who diagnose, treat, or work with patients with psychiatric conditions

Methods of Presentation: Powerpoint visual and written notes with the ability to take notes (reading/writing/visual), case study (kinesthetic), voicethread (auditory)

Objectives

1. Introduce the state of the science for the diagnosis and treatment of mental illness
2. Introduce the concept of personalized medicine and pharmacogenomics.
3. Introduce pharmacogenomics as they relate to psychiatric mental health care treatment
4. Address current trends and science in regards to pharmacogenomics
5. Introduce practical clinical experience utilizing pharmacogenomics as a psychiatric mental health care nurse practitioner
6. Introduce the utility of pharmacogenomics for health practitioners

Learning Outcomes

By the end of the presentation the learner will:

1. Understand the importance of pharmacogenomic testing
2. Have a general understanding of how genotype and phenotype relate to treatment
3. Be able to identify current phenotypes associated with mental illness as it relates to genotype
4. Have a general understanding of how to apply medication treatment based on genotype and phenotype

Risk Factors for Mental Illness

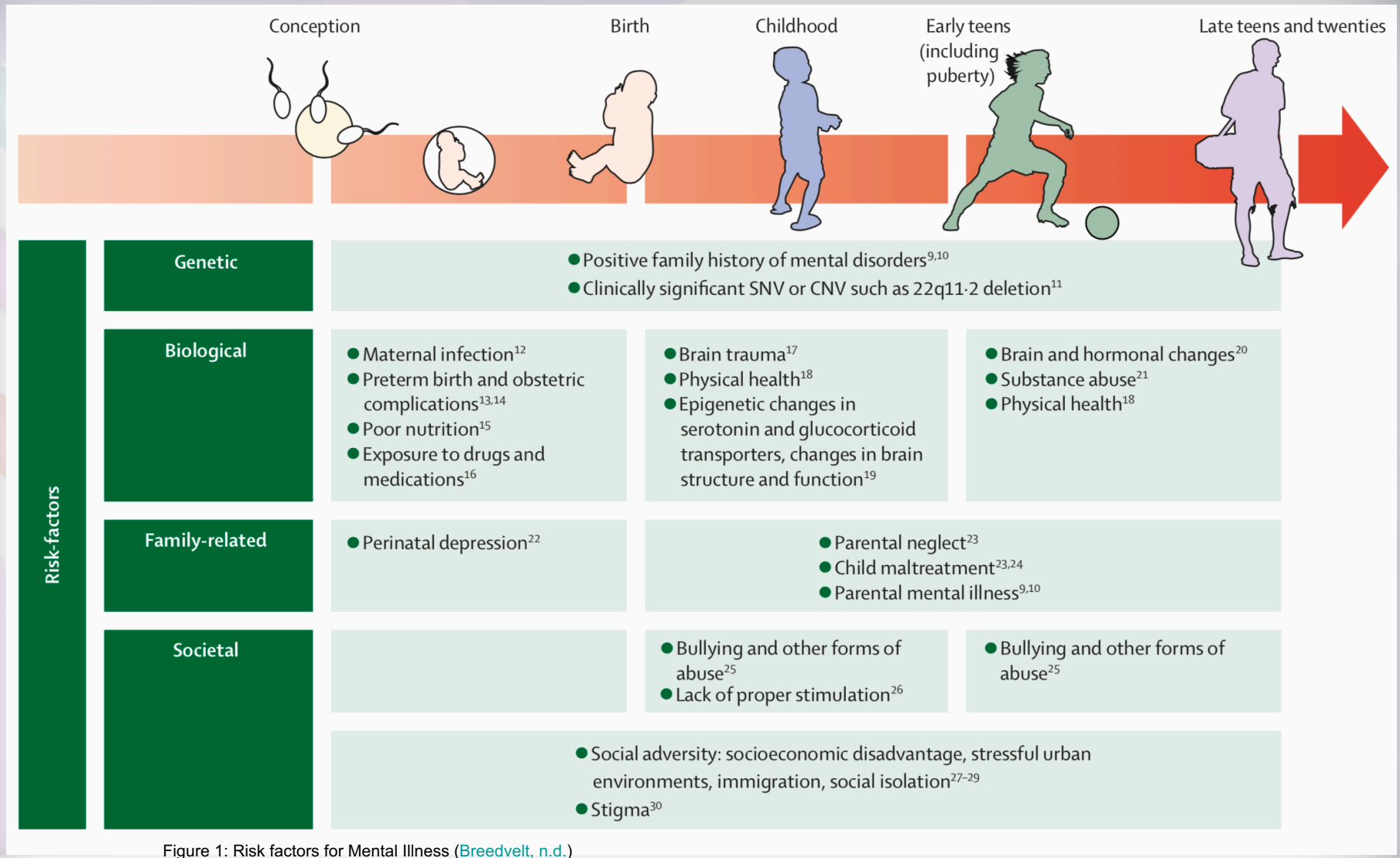


Figure 1: Risk factors for Mental Illness (Breedvelt, n.d.)

(Arango et al., 2018)

Let's assume we had a perfect medical workup we are certain of psychiatric illness

Figure 8: Delusions (istiockphoto, n.d.)

(istockphoto, n.d.)

Rosenhan (1973)

- Aim: Test the reliability of psychiatric diagnoses
- Study 1: Researchers pretended to hear voices (all but 1 diagnosed with schizophrenia) and stayed in hospital approx 19 days; considered abnormal
- Study 2: Warned hospital that normal people would be pretending to be abnormal; not true; hospital mistook abnormal people to be normal people faking it

Rosenhan (1973)

- Conclusion: It is not possible to distinguish between sane and insane in psychiatric hospitals
- Medical diagnoses can be made with a lack of scientific evidence
  - Ethical issue: Are treatments properly justified?

Figure 11: Rosehan2 (Mackenzie, 2014)

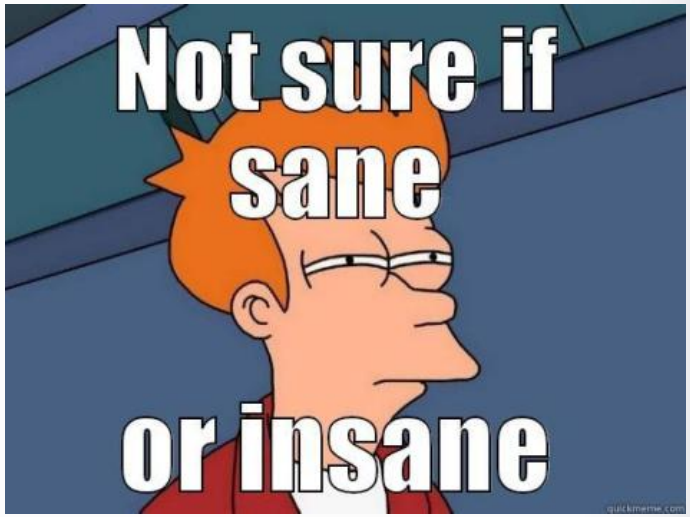


Figure 12: Futurama (Iszlschoolnewspaper, n.d.)

(Mackenzie, 2014)

Rosenhan (1973) Study Concludes Dxs Made With Lack of Scientific Evidence

Unreliable

- Diagnostic systems have been accused of being unreliable
- With the same manual, two psychiatrists could diagnose the same patient with two different disorders
- Beck et al. (1962): Agreement on diagnosis for 153 participants between two psychiatrists was only 54%

Figure 13: Unreliable (Mackenzie, 2014)

(Mackenzie, 2014)

"The *DSM-5* is a less than ideal approach to clinical diagnosis is evident. It is purely phenomenological and largely arbitrary, and not based on valid etiological concepts or mechanisms of illness or genetic predispositions," (Weinberger, Glick, & Klien, 2015, p. 1161).

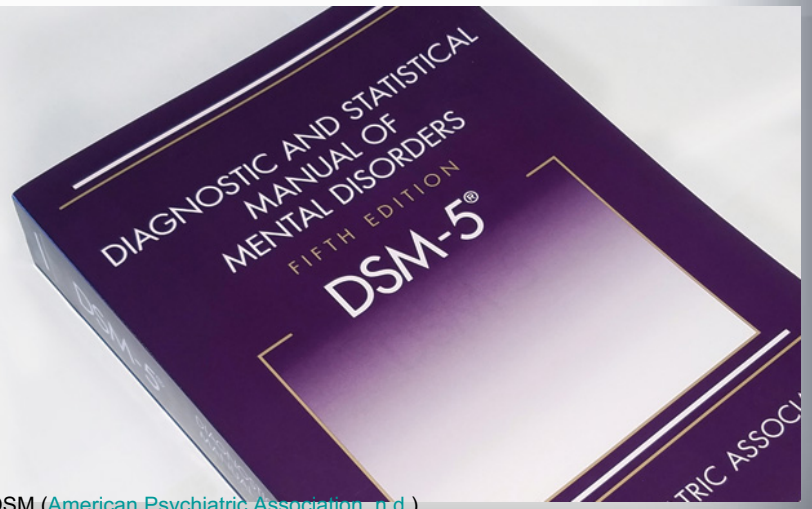
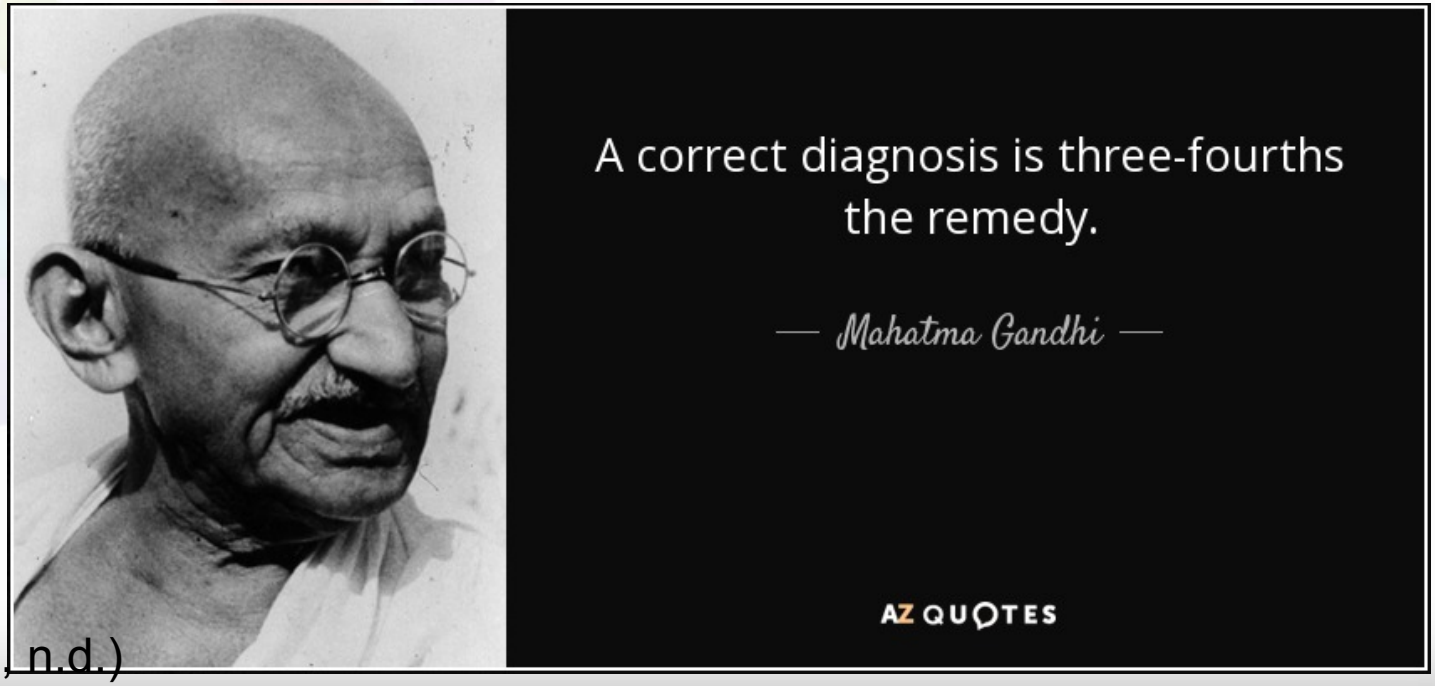


Figure 10: DSM (American Psychiatric Association, n.d.)

Now Treatment!

- Now let's assume we had a perfect psychiatric workup and now we are certain of the psychiatric illness…



(Azquotes, n.d.)

Figure 14: Ghandi (AZQuotes, n.d.)

Current Medication Perspectives – Examples Depression

Best Practices Treatment Guideline for Depression

Based on 2010 APA Practice Guidelines and NeuroStar TMS Therapy® Indication for Use.[1]

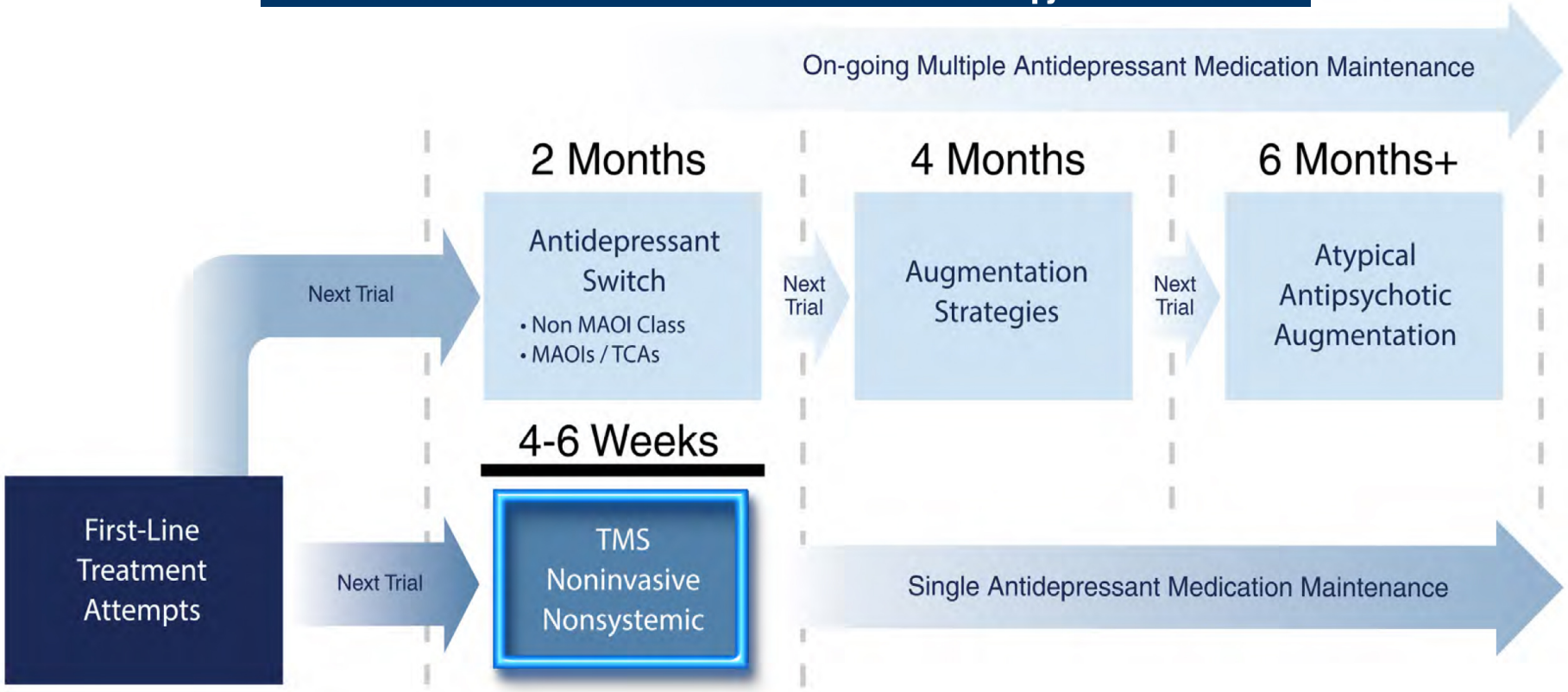


Figure 19: Guideline (SIA, n.d.)

Systemic Drug Side Effects[2]

Most common side effects per antidepressant medication labels (5% and 2x placebo)

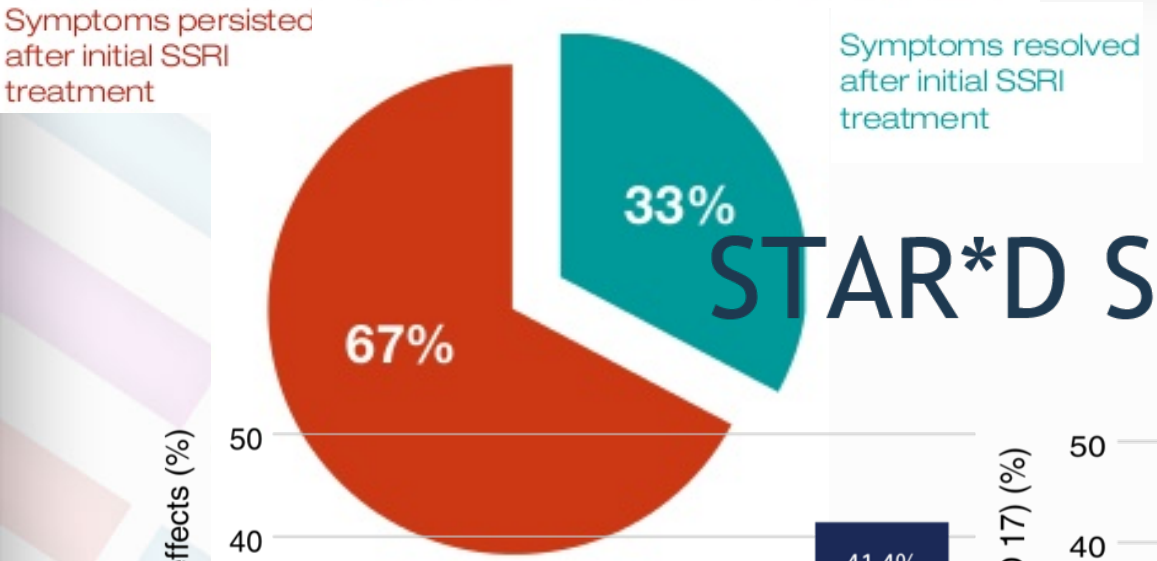
Insomnia	Weight Gain	Nervousness	Drowsiness	Anxiety	Tremor
Blurred Vision	Nausea	Constipation	Weakness	Impotence	Abnormal Ejaculation
Dry Mouth	GI Distress	Diarrhea	Dizziness	Sweating	Decreased Sexual Interest
Fatigue	Sexual Dysfunction	Headache/ Migraine	Increased Appetite	Decreased Appetite	Treatment Discontinuation Side Effects

(TMSNeurosolutions, n.d.)

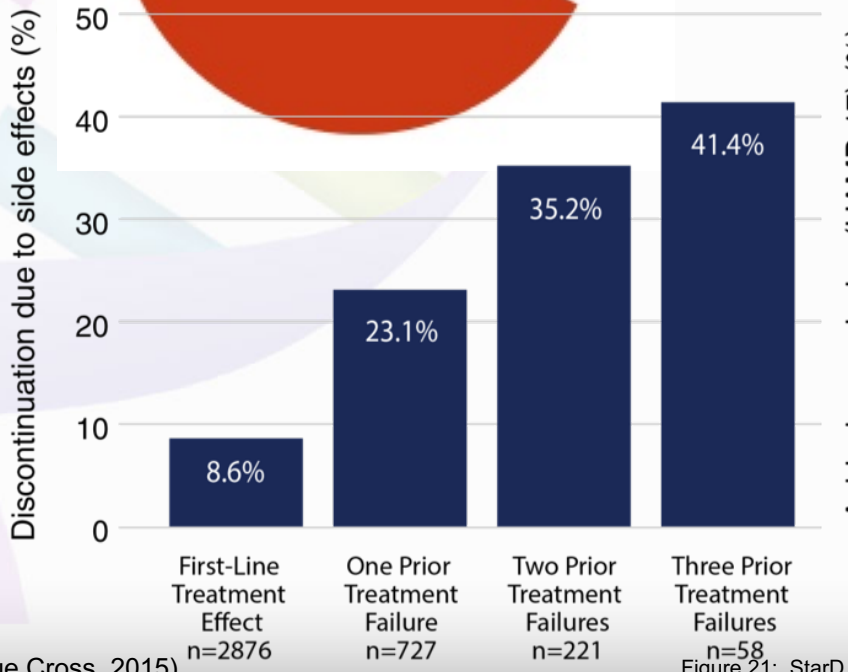
Current Medication Perspectives – Examples Depression

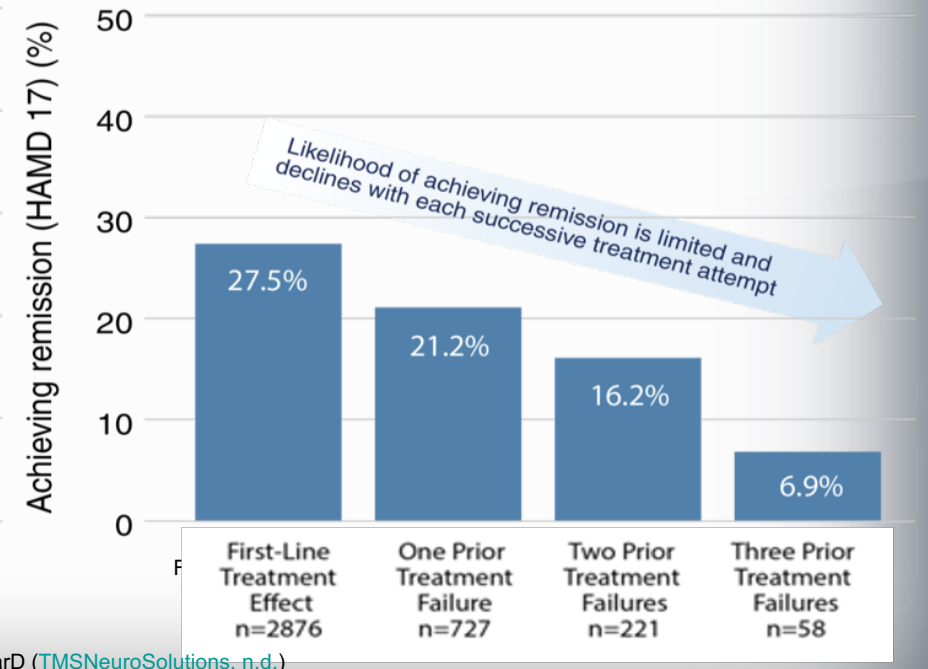
Mental health

Only 33% of patients respond to 1st line of treatment for depression



STAR*D Study





(Medavie Blue Cross, 2015)

Figure 21: StarD (TMSNeuroSolutions, n.d.)

Current Medication Perspectives

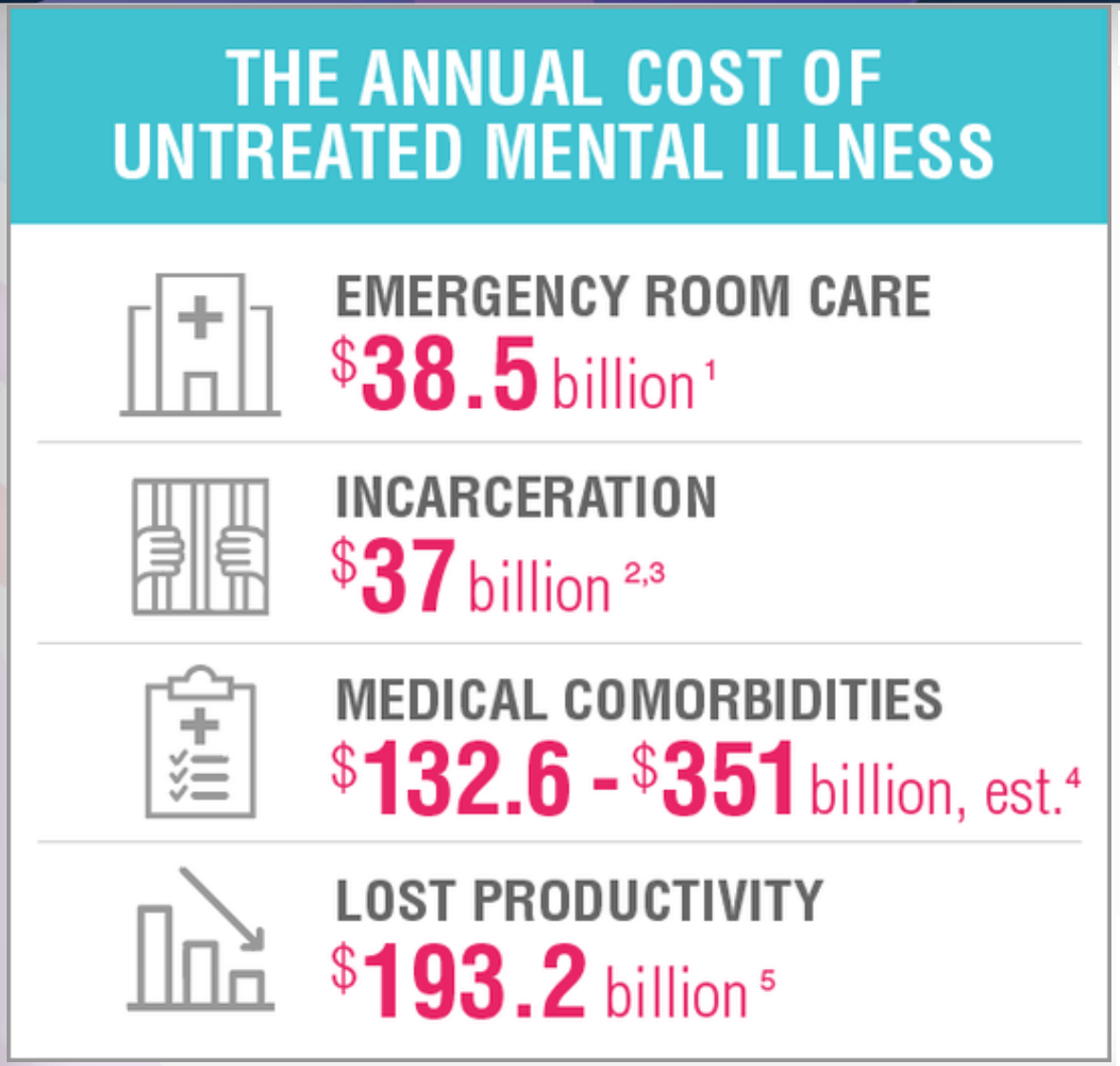


Figure 23: Untreated (Valant, 2017)

Figure 22: Utilization (Medavie Blue Cross, 2015)

(Medavie Blue Cross, 2015) (Valant, 2017)

Current State of Diagnosis and Management of Psychiatric Illness

- Flaws in the system – leading to poor outcomes and increased costs to the system
  - Diagnostic methods
    - The DSM is largely arbitrary and there is too much overlap in symptoms for the criteria of our illnesses as described in the DSM.
    - Diagnosis relies on a system where both provider and patient are communicating clearly and efficiently
  - Treatments
    - Limited in efficacy & increased side effects
    - Increased stigma
    - Decreased adherence

Conclusion for the Current State of the Science:

If we are going to continue to diagnose and treat mental illness, We need better science

(Abzu2, 2015)

Figure 24: Science (Abzu2, 2015)

A Better Approach RDoC

- "Research Domain Criteria (RDoC) is a research framework for new approaches to investigating mental disorders. It integrates many levels of information (from genomics and circuits to behavior and self-reports) in order to explore basic dimensions of functioning that span the full range of human behavior from normal to abnormal," (NIH, n.d.).

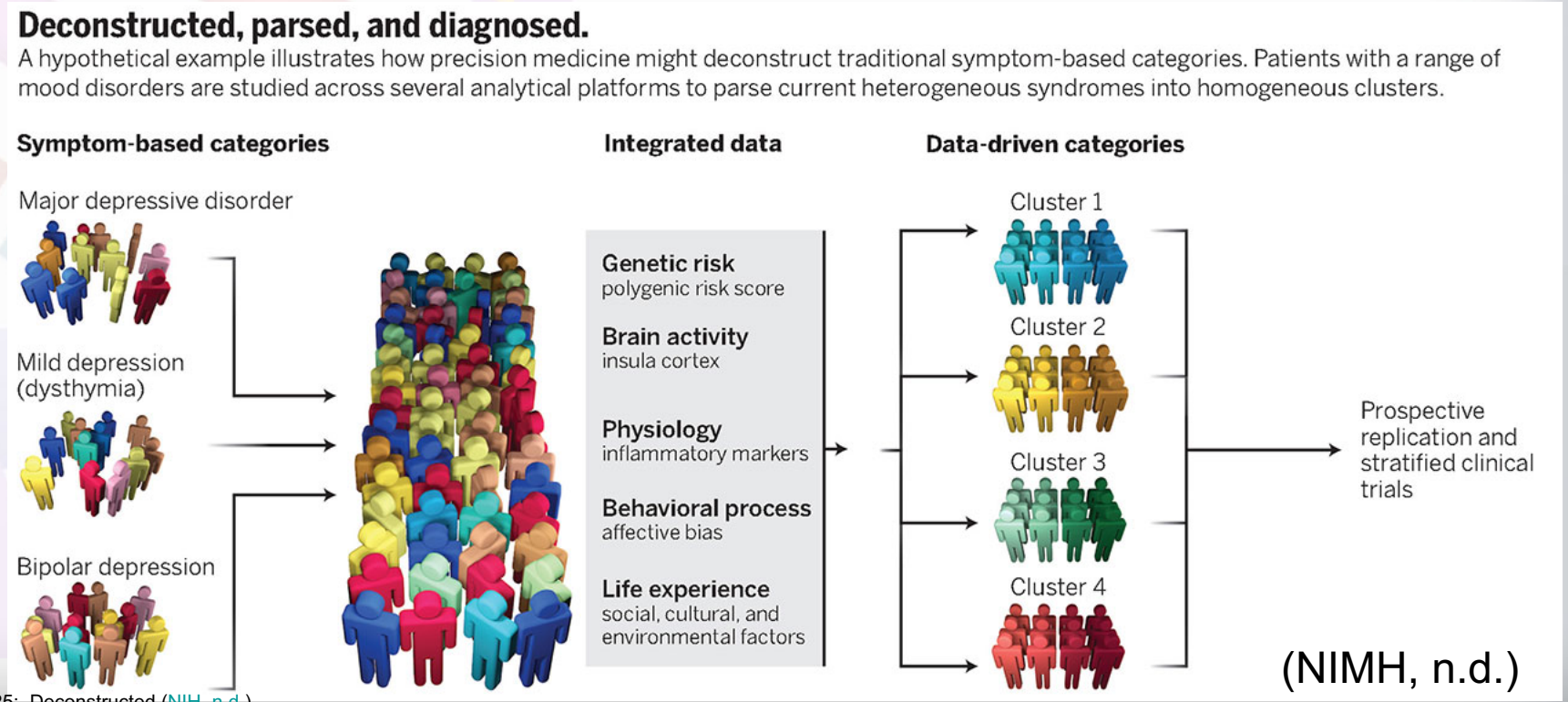


Figure 25: Deconstructed (NIH, n.d.)

What is Personalized Medicine? What is Genomic Medicine?

Traditional Clinical DX & Mgmt.

- Focuses on clinical signs and symptoms, medical histrory, lab values, imaging to diagnose and treat.
- REACTIVE APPROACH

Figure 32: Med Helix (Genome, n.d.)

Personalized Medicine

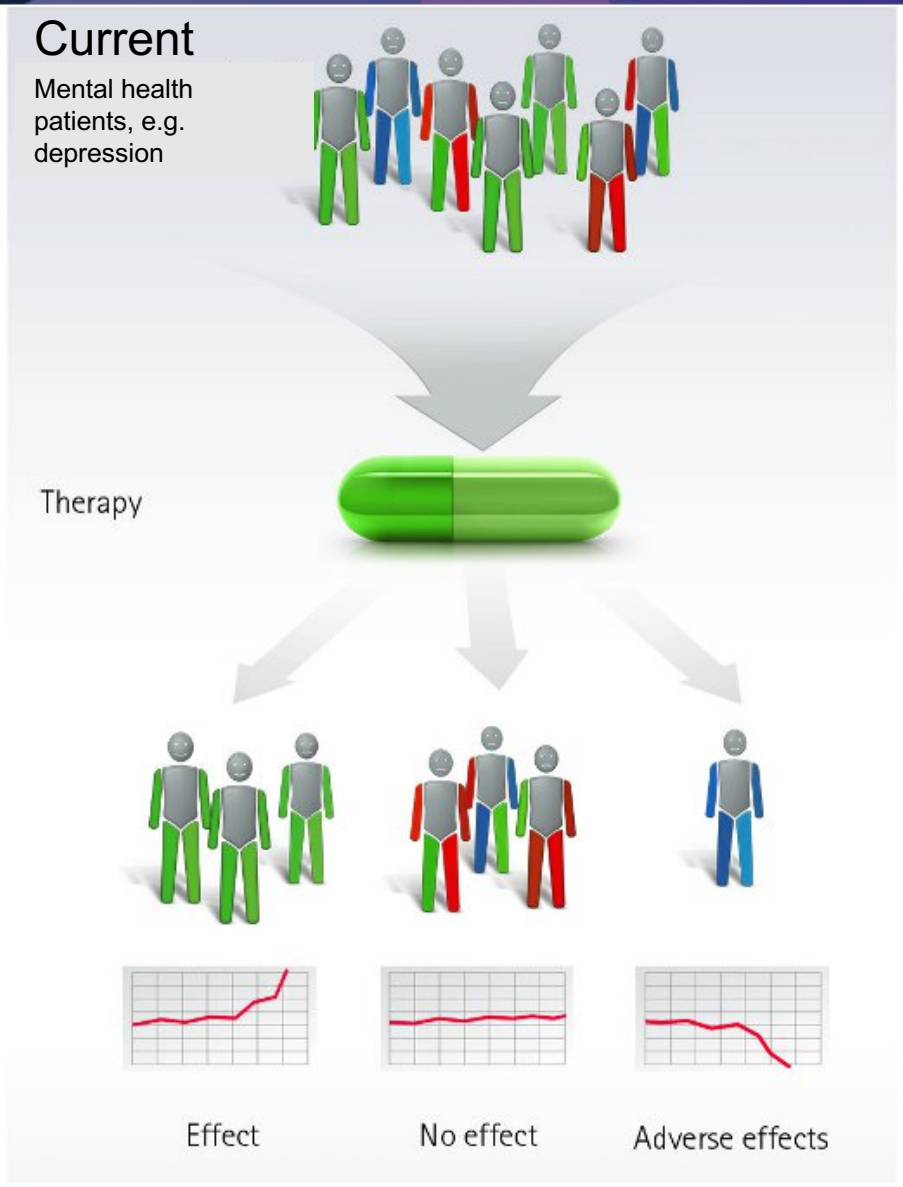
- Proposes customization of healthcare
- Tailored to the individual patient
- Diagnostic testing essential for selecting apppropriate therapies

Figure 31: DNA Helix (Molten, 2017)

Genomic Medicine

- Uses genomic information as part of clinical care
- For Diagnostic or therapeutic decision making

Why Personalized Medicine?



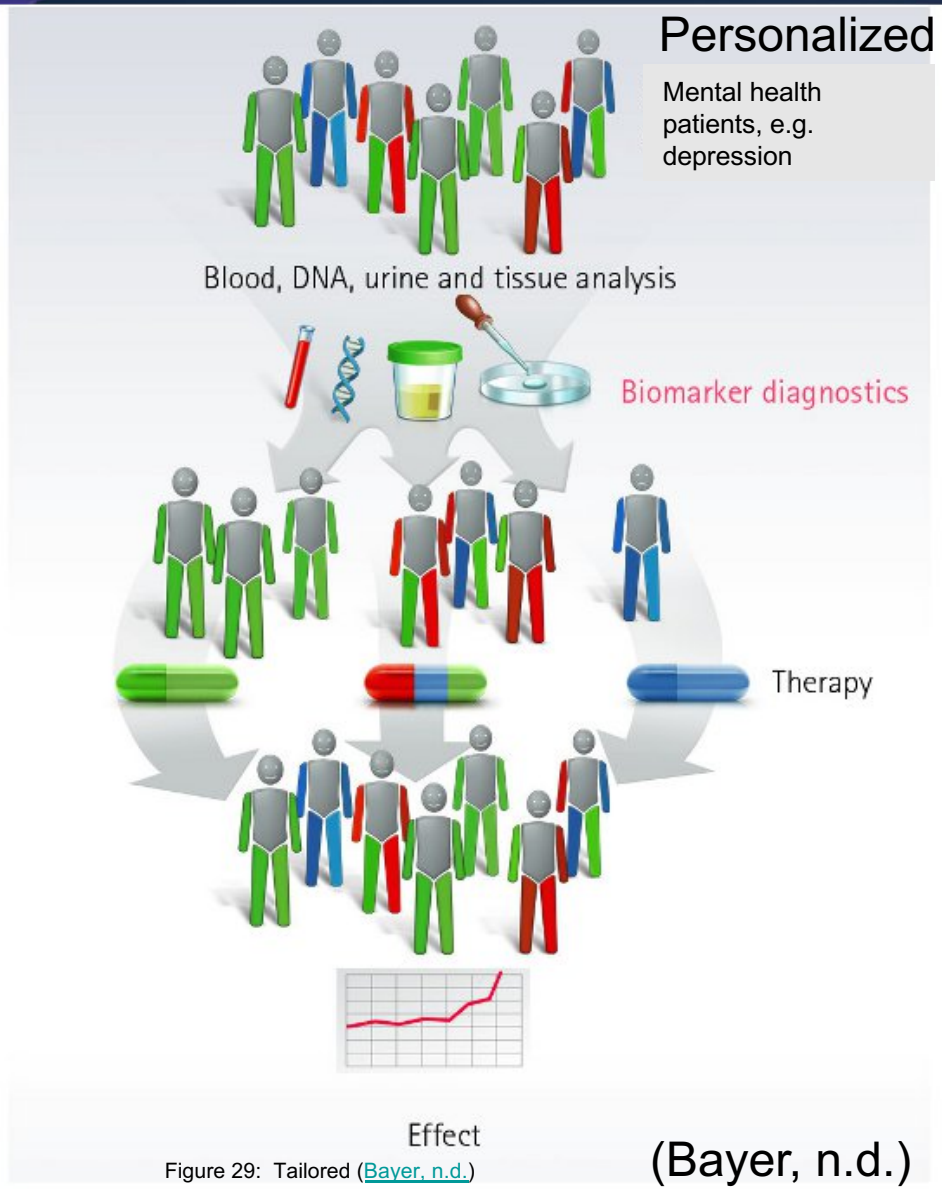


Figure 29: Tailored (Bayer, n.d.)

(Bayer, n.d.)

Personalized Medicine: A Better Approach with Genomics

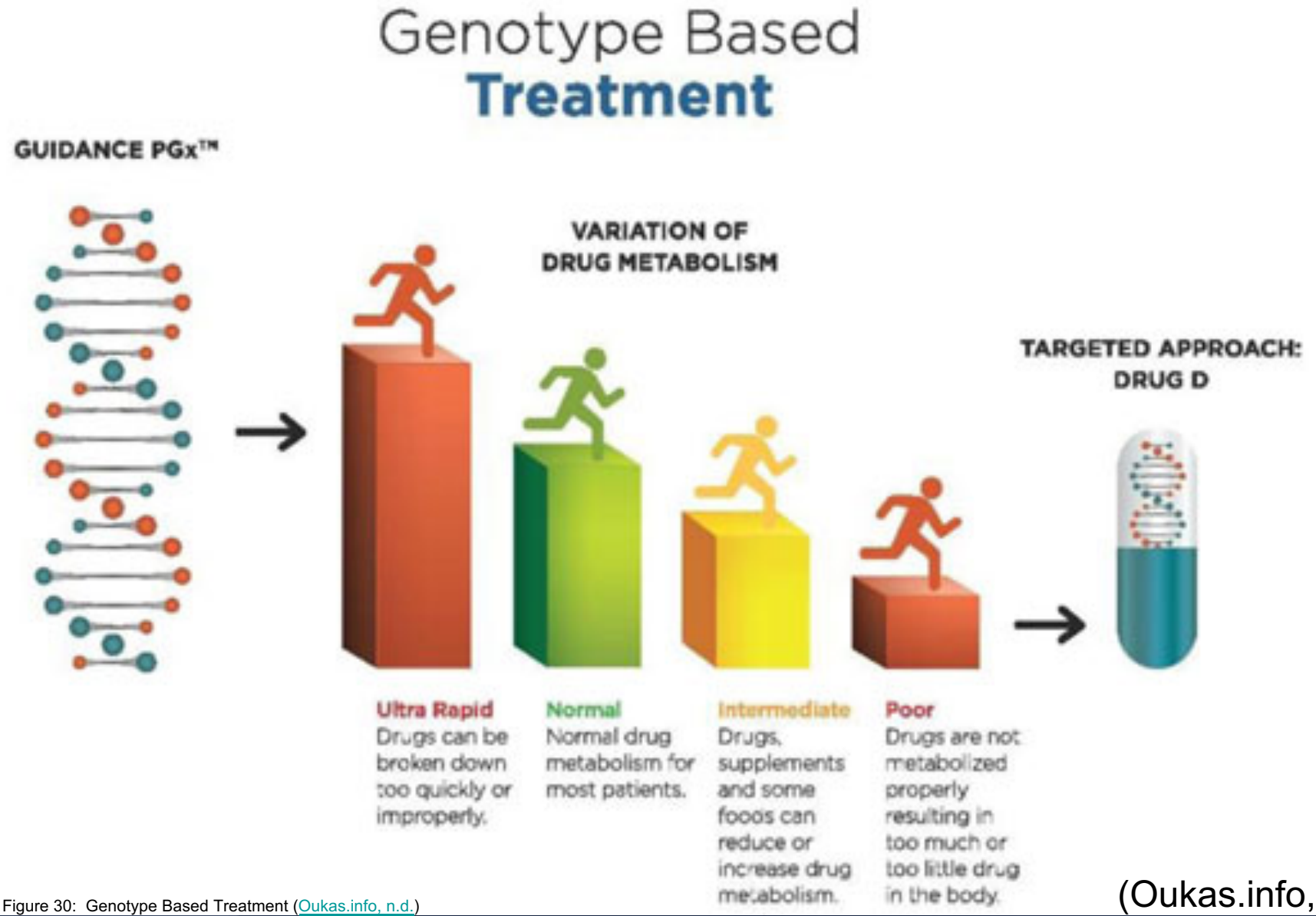


Figure 30: Genotype Based Treatment (Oukas.info, n.d.)

(Oukas.info, n.d)

Genetics 101: Monogenic Inheritance

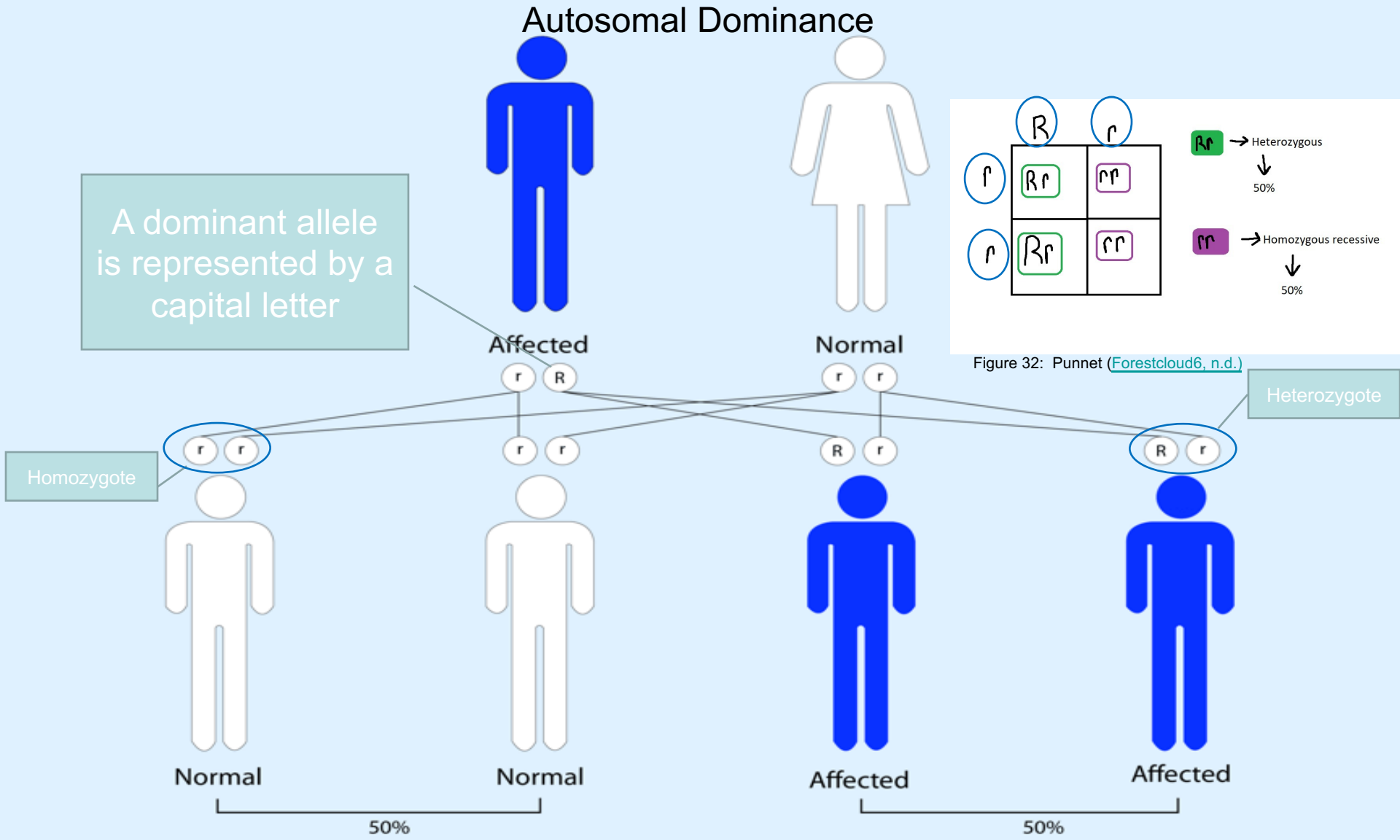
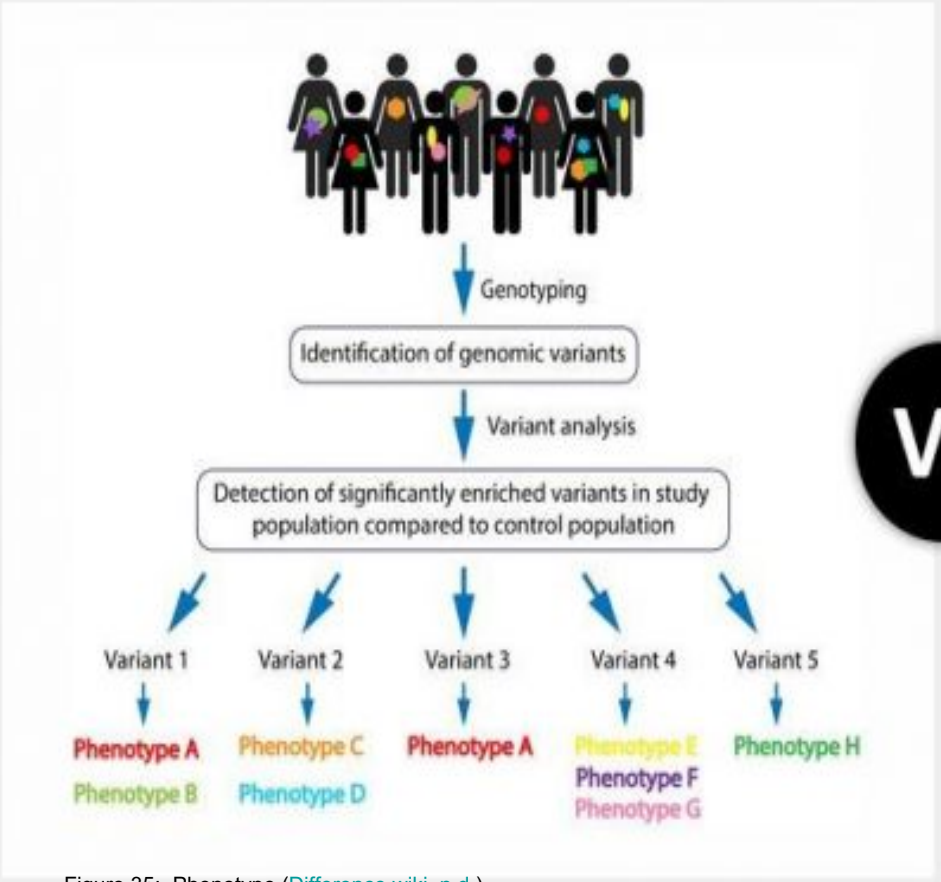


Figure 29: Tailored (Bayer, n.d.)

Figure 32: Punnet (Forestcloud6, n.d.)

Genetics 101: Genotype vs. Phenotype



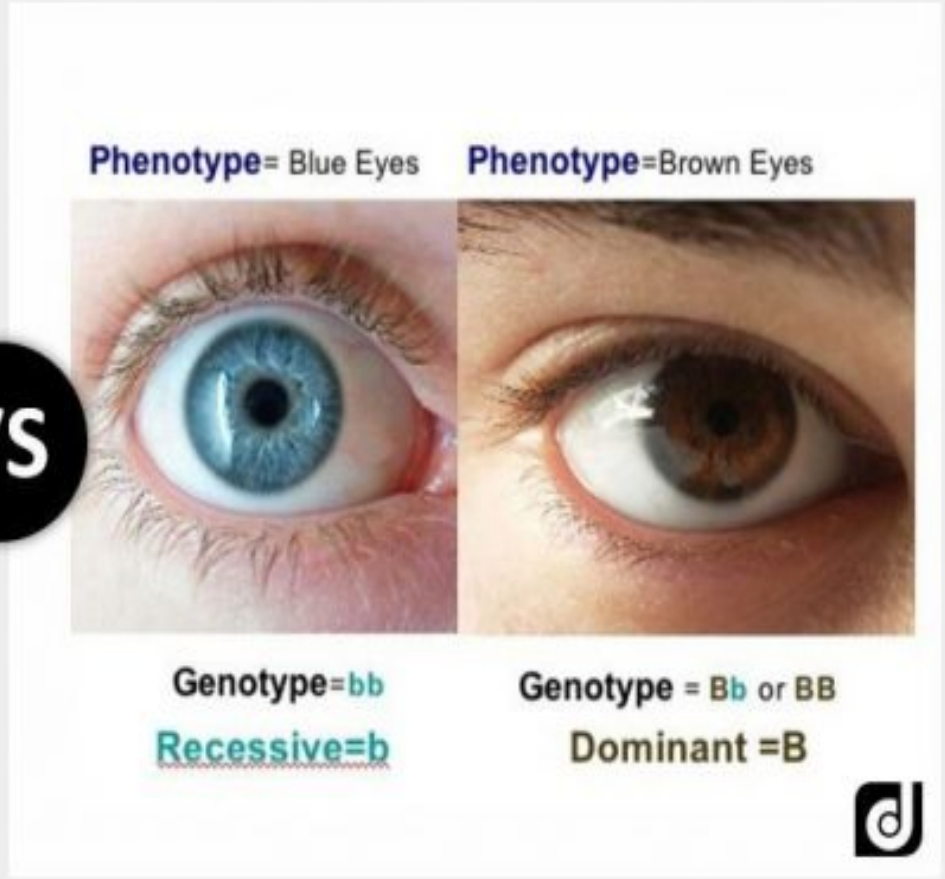


Figure 35: Phenotype (Difference.wiki, n.d.)

Genotype vs. Phenotype

(Difference.wiki, n.d.)

Gene Testing Environment

- Most genetic tests focus on single gene variant and do not synthesize information from multiple gene variants and confounding factors when our bodies are more complex than single gene variants (Bosworth, 2018).

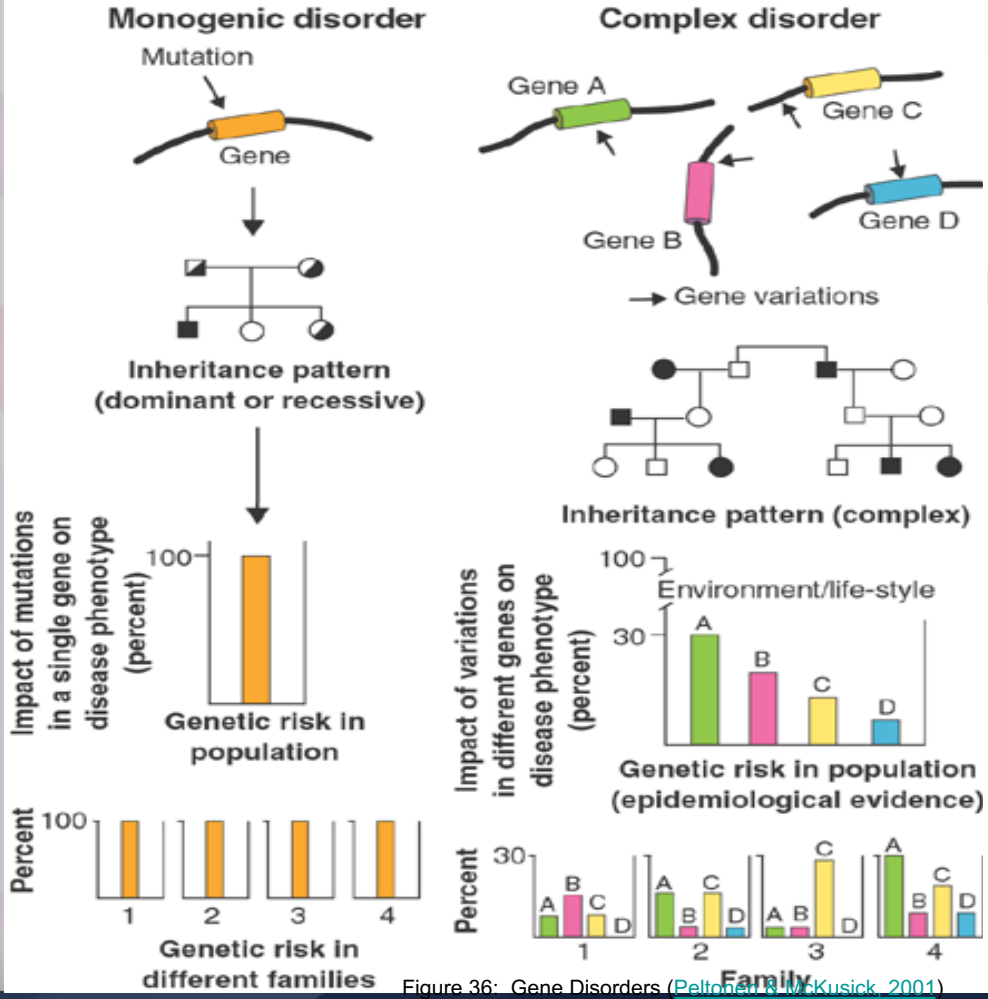


Figure 36: Gene Disorders (Peltonen & McKusick, 2001)

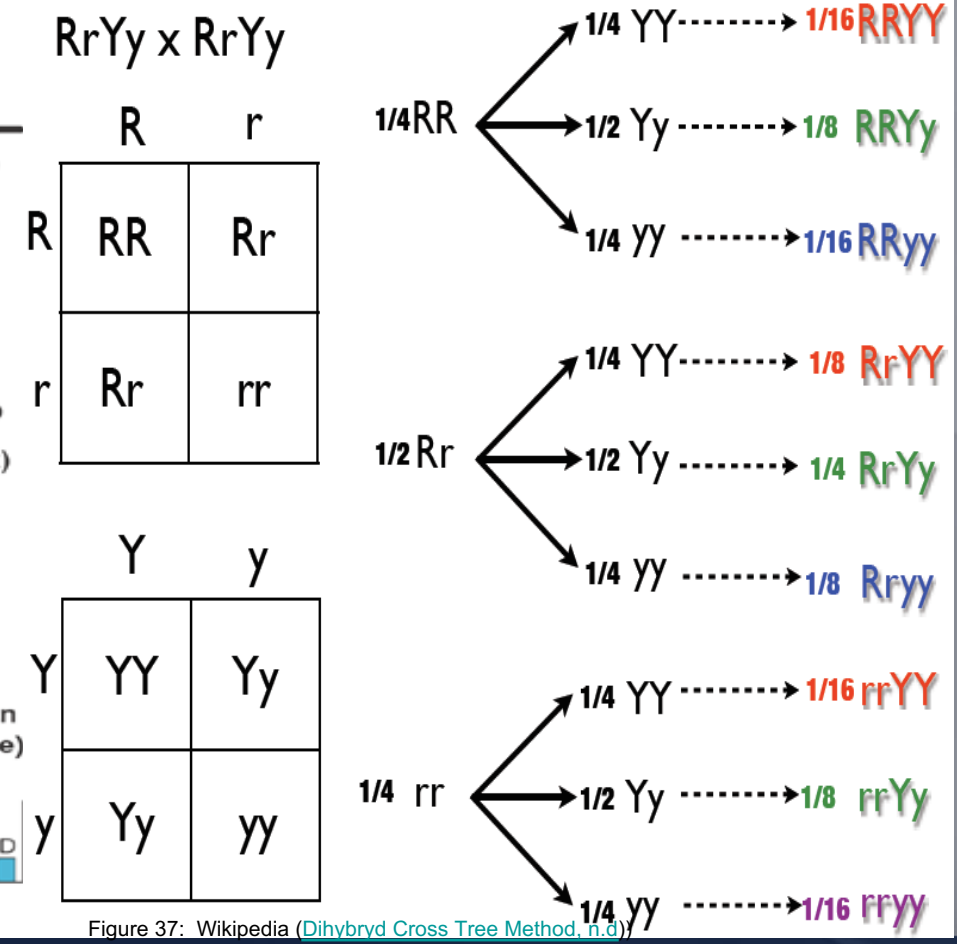


Figure 37: Wikipedia (Dihybryd Cross Tree Method, n.d)

Current Diagnosis & Treatment Gaps in Psychiatry- Explained by Genetics (Genetic Overlap)

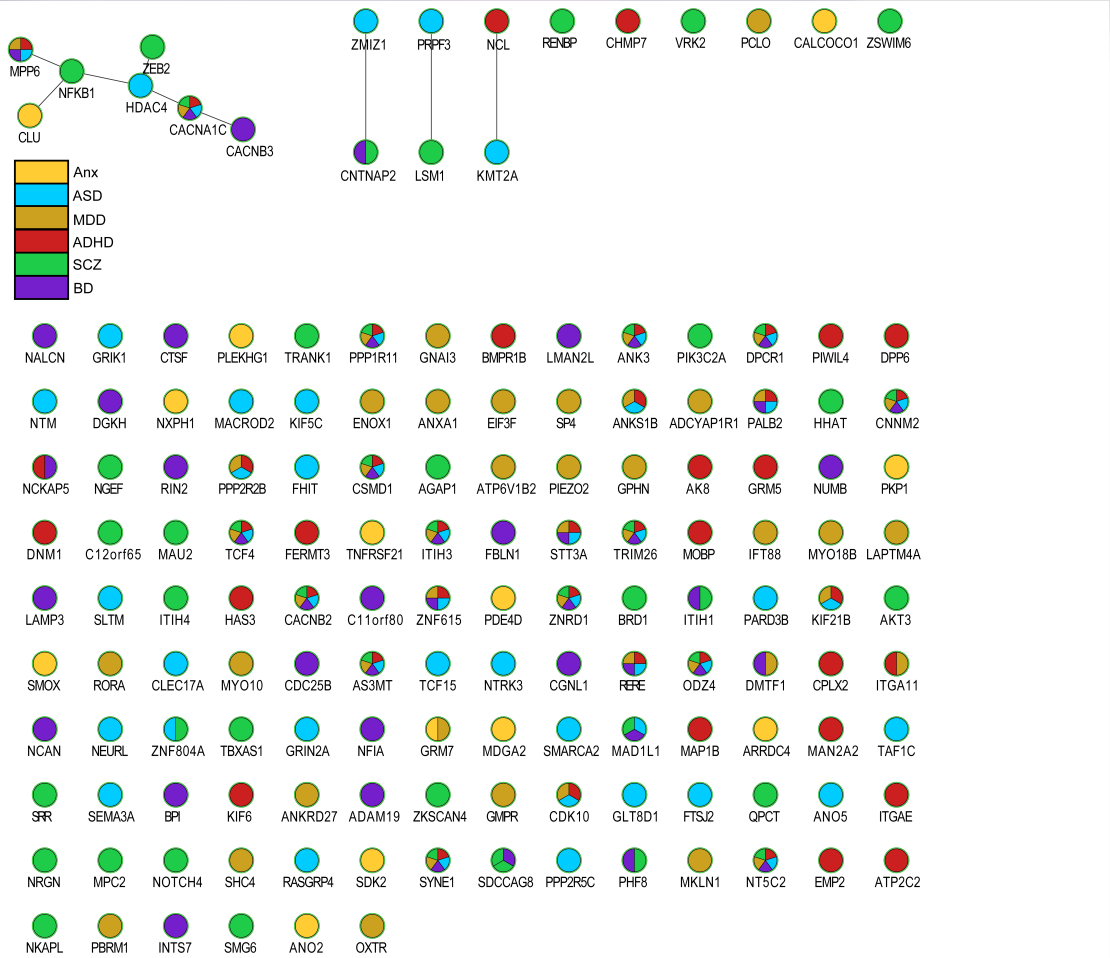
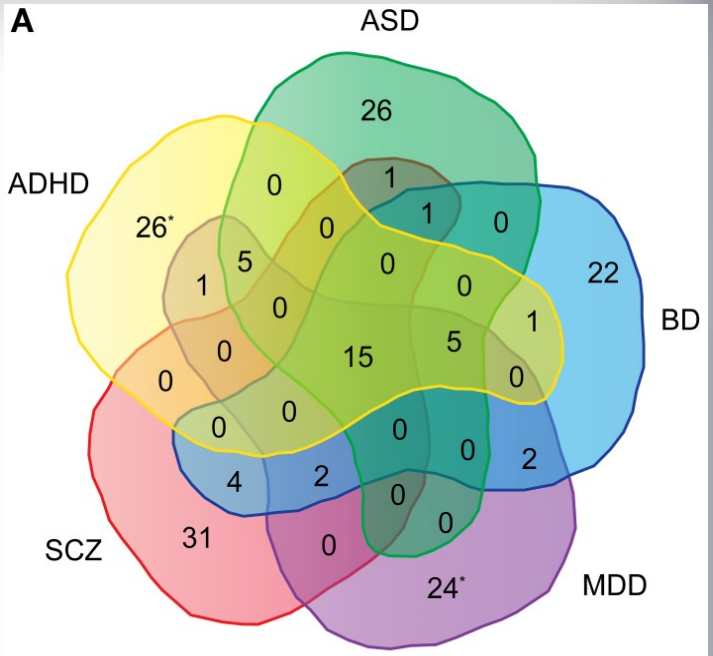


Figure 26: Overlap (Lotan et al., 2014)



B

Genes shared among	N genes
6 disorders	0
5 disorders	15
At least 4 disorders	20
At least 3 disorders	28
At least 2 disorders	39

(Lotan et al., 2014)

Venn diagram depicting the overlap of genes across multiple disorders. (A) For each disorder (ADHD, ASD, BD, MDD, SCZ) the overlap of top-51 SNPs with associated protein-coding genes is depicted. For anxiety only 16 protein-coding genes could be retrieved, one overlaps with ADHD and one with MDD. **(B)** Summary of the number of genes shared among disorder.

Using Genetics to Personalize Treatment

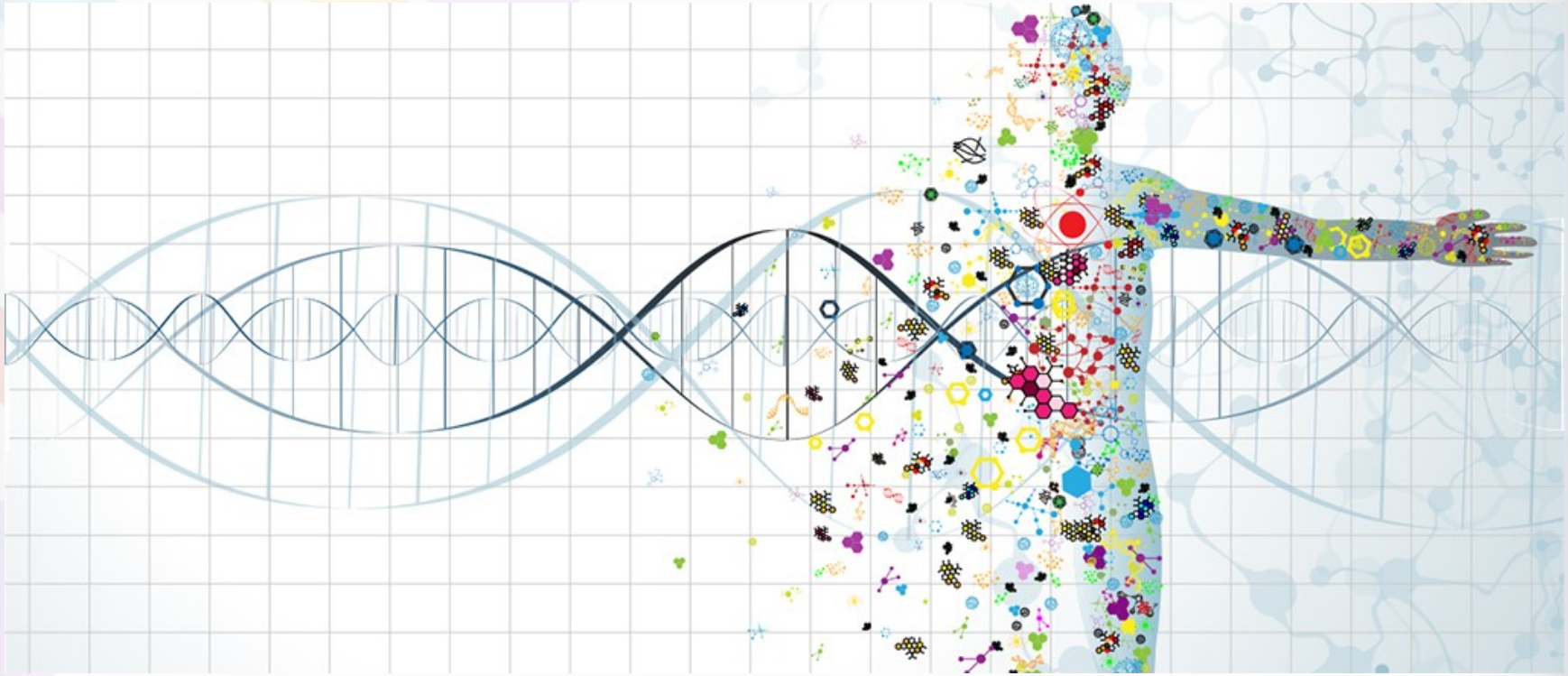


Figure 39: Precision (SAP, 2016)

Now it is important to understand the importance of genetic overlap and application to treatment.

Pharmacodynamics

Pharmacodynamics = what the drug does to the body

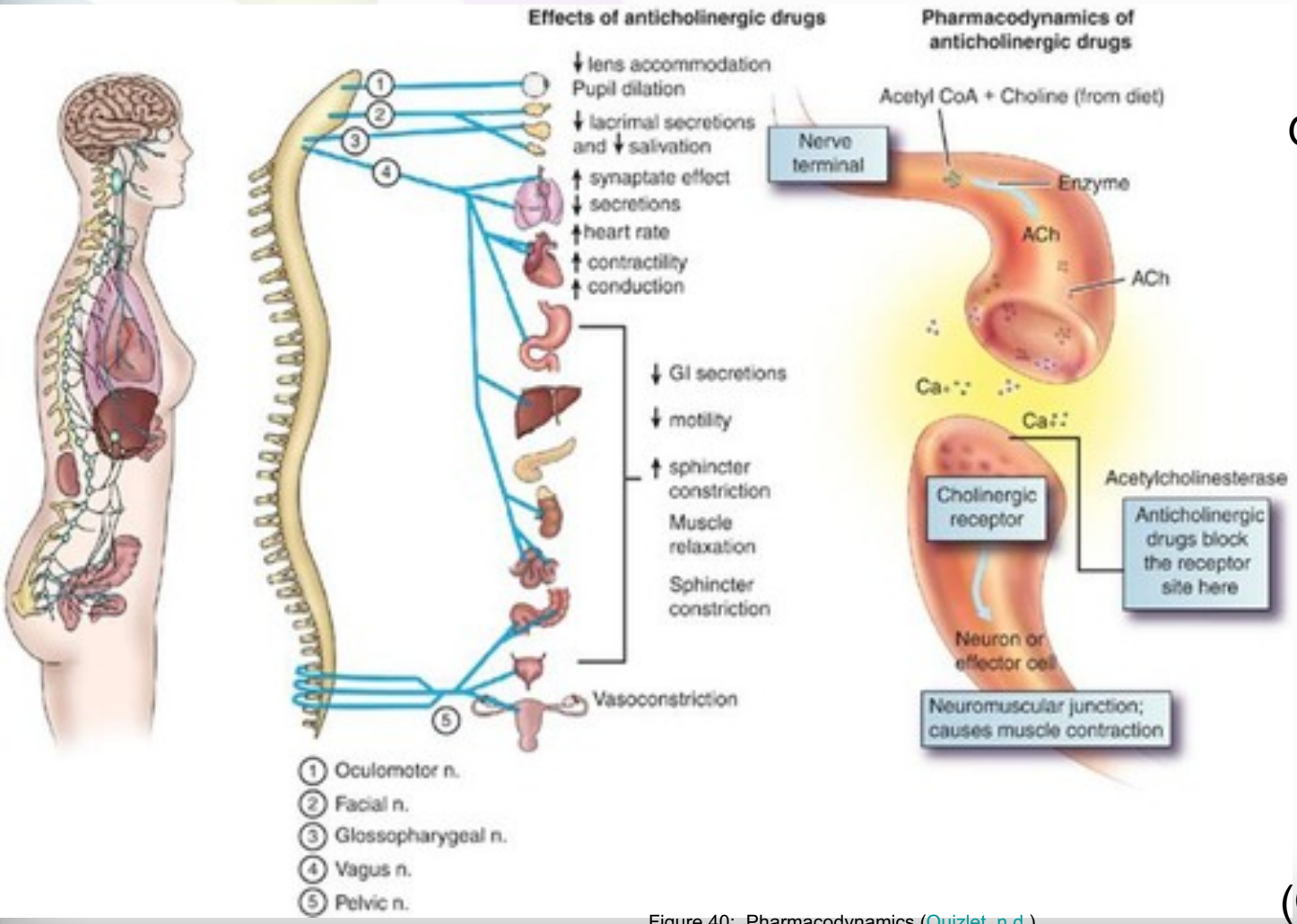


Figure 40: Pharmacodynamics (Quizlet, n.d.)

Genes to cover:

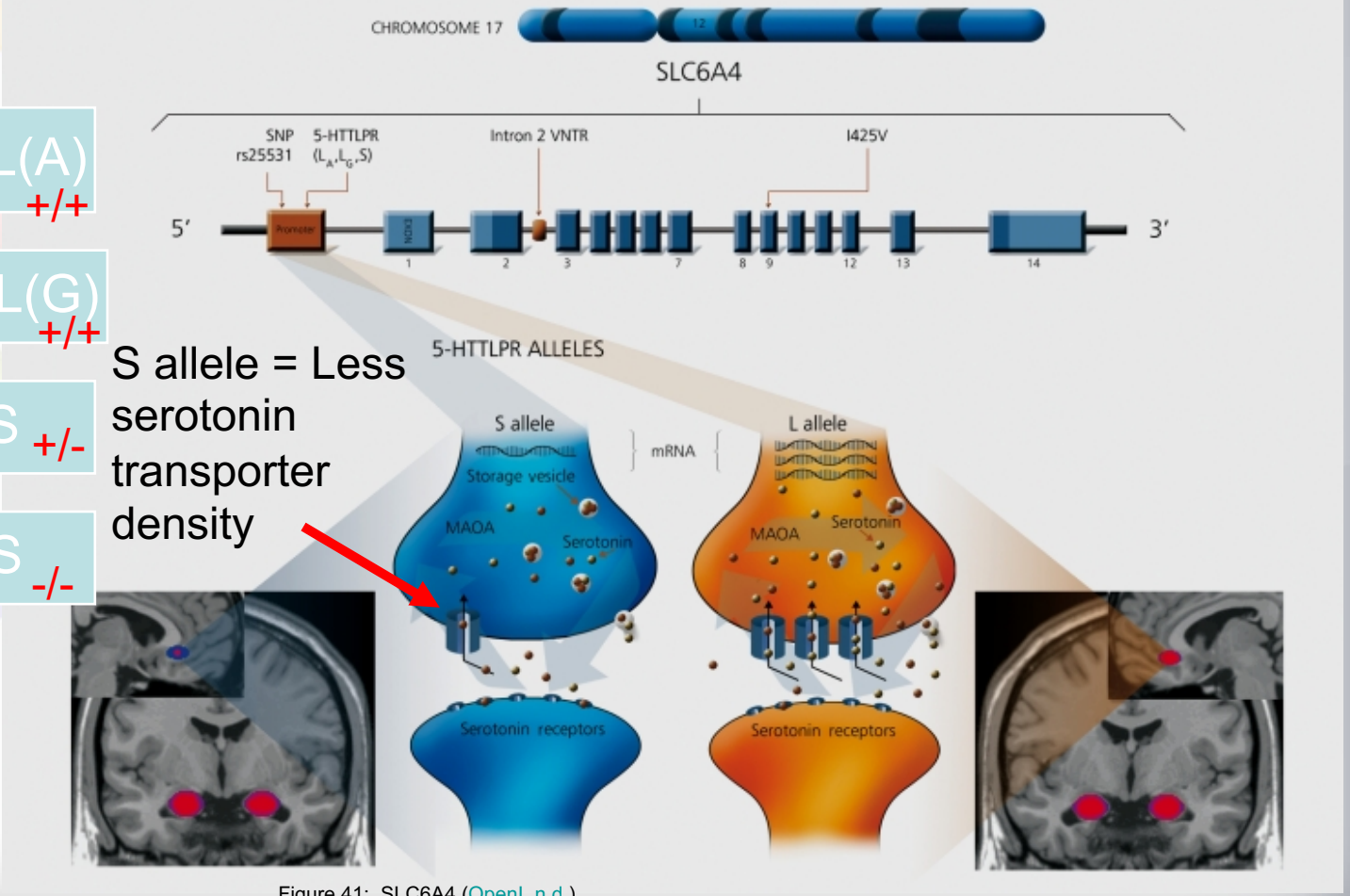
- SLC6A4
- 5HT2C
- MTHFR
- CACNA1C
- ANK3
- MC4R
- DRD2
- COMT
- ADRA2A
- BDNF
- OPRM1
- GRIK1

(Quizlet, n.d.)

SLC6A4

SLC6A4

- L(A) L(A) +/+
- L(G) L(G) +/+
- L/S +/-
- S/S -/-



S allele = Less serotonin transporter density

Figure 41: SLC6A4 (Openl, n.d.)

SLC6A4

The **L(A) variant** is generally associated with a **better antidepressant response** in Caucasian patients. In a meta analysis by Serre tti et al, L carriers had better response and remission rates within 4 weeks of antidepressant treatment when compared with subjects with the SS genotype.

A common A>G functional polymorphism within the L allele has also been identified. The G variant of this polymorphism (LG) shows transcription levels similar to the S allele, whereas the A genotype (LA) shows higher expression levels. In the STAR*D study they reported a significant association between the **LA allele and reduced adverse events** in the white nonhispanic population, but not with treatment outcome

Additionally, the **short/short** genotype of a polymorphism (5-HTTLPR) in the serotonin transporter gene was associated with **greater cortisol reactivity** in Study 1 as well as in Study 2 (previously reported). The Cys23Ser polymorphism and the 5-HTTLPR were independently associated with cortisol reactivity. Demonstrate increased **neuroticism, anxiety, negative emotionality, panic disorder, social phobia, increased depression and suicide.**

(Gerresten, Muller, Tiwari, Mamo, & Pollock, 2009) & (Way, Brown, Quaglia, McCain, Taylor, 2016) (Murphy et al., 2008)

SLC6A4: SSRIs & Cortisol

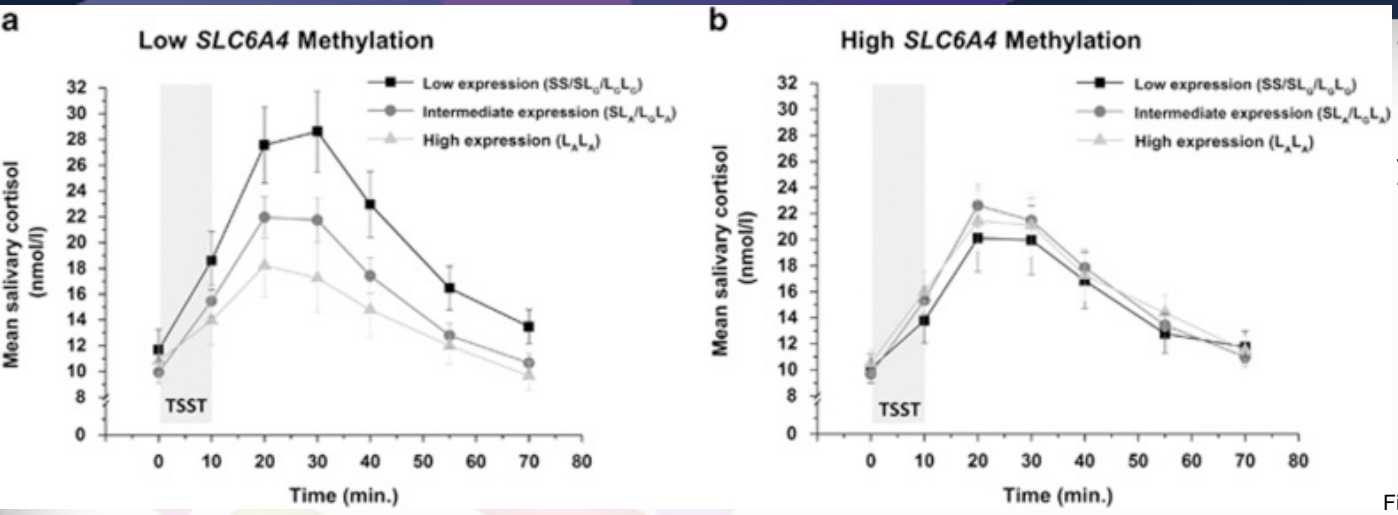


Figure 42: Cortisol (Murphey et al., 2008)

This figure shows that the **S/S or -/-**carriers have **higher cortisol reactivity** in the context of stress compared to single S carriers or L/L +/+ carriers

Figure 44: SLC6A4 Methylation (Alexander et al., 2014)

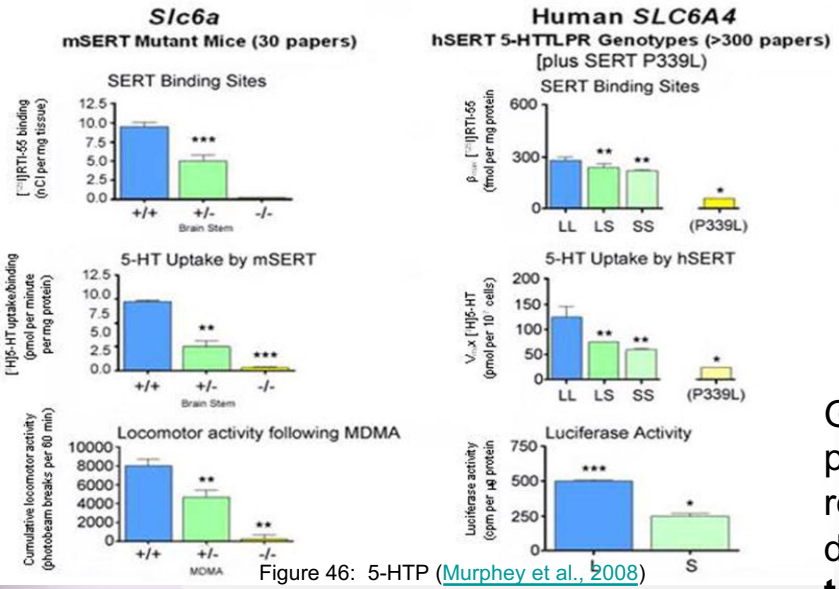
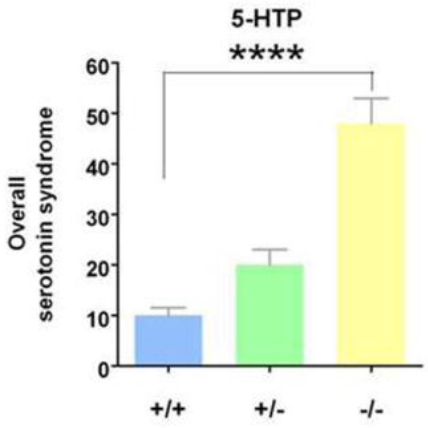
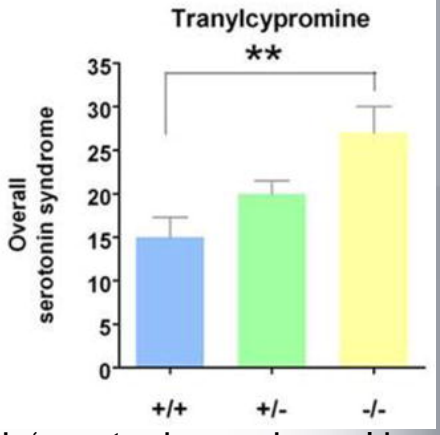


Figure 46: 5-HTP (Murphey et al., 2008)





Genetic vulnerability to an exaggerated, 'serotonin syndrome' is present in *Slc6a4* L/S and *Slc6a4* S/S. One of the most remarkable group of drug response alterations observed in SERT-deficient mice are **serotonin syndrome behaviors** and **temperature changes** produced by serotonin agonists (Fox et al., 2007b; Fox and Murphy, in press).

SS = less responsive to SSRIs

5HT2C

5HT2C

- C or C / C
- T or C / T

Increases risk of weight gain with atypical antipsychotics. Possible increase of anxiety.

T allele is protective against atypical antipsychotic weight gain

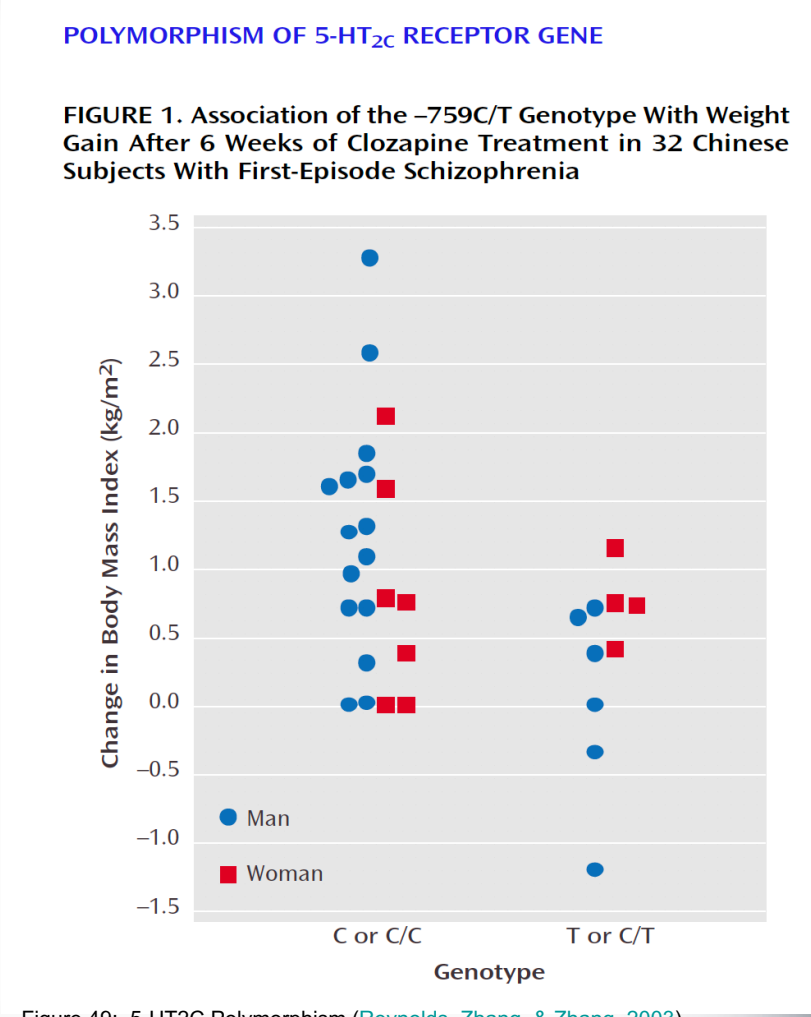


Figure 49: 5-HT2C Polymorphism (Reynolds, Zhang, & Zhang, 2003)

(Del Castillo, Zimmerman, Tyler, Ellngrod, & Calarge, 2013)

MTHFR C677T

MTHFR C677T

- C / C
- C / T
- T / T

(National Institute of Health, n.d.)

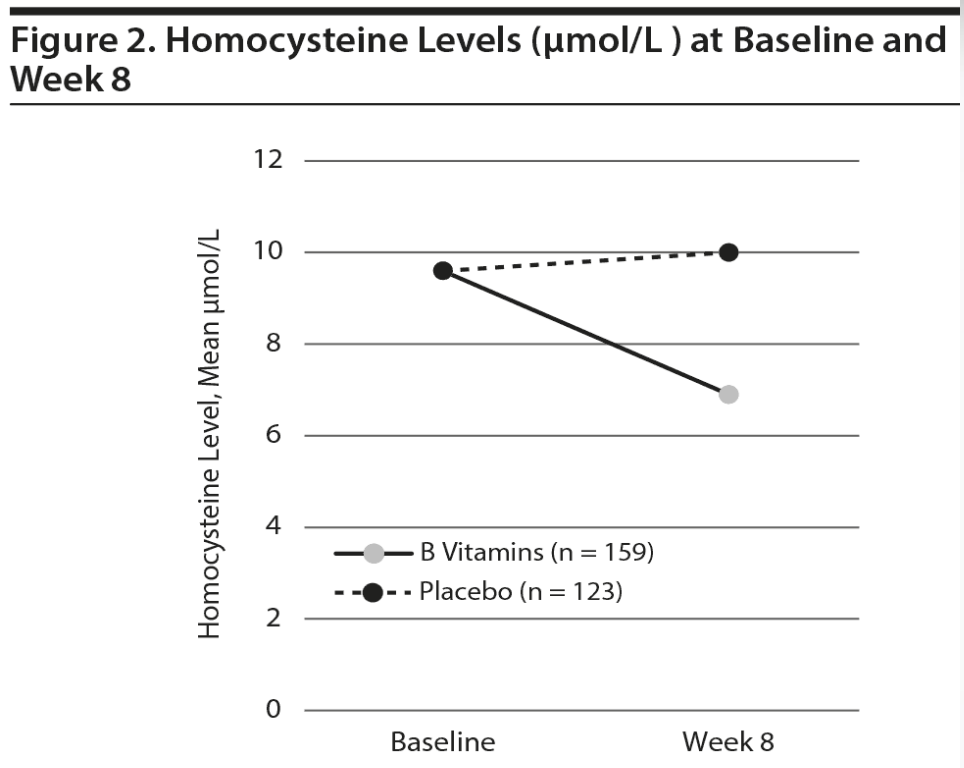


Figure 53: Homocysteine Levels (Mech & Farah, 2016)

T allele is more frequently associated with unipolar depression, bipolar disorder, schizophrenia, and autism. Increased risk of hyperhomocystenemia. Increased risk of having children with neural tube defects. Studies suggest that women with two C677T gene variants are **twice as likely** to have a **child with a neural tube defect**.

MTHFR A1298C

- A / A
- A / C
- C / C

The gene is compromised about 70% in MTHFR A1298C (A/A) individuals, and about 30% in people with a heterozygous (A/C) mutation.

A1298C SNP has been associated with ADHD. The 1298CC MTHFR genotype has been observed to be associated with DNA hypomethylation status. C / C allele is more frequently associated with depression than those with A /A.

(MTHFR Treatment., n.d.) (Geneticgenie, n.d.)

MTHFR and L-methylfolate & B-Vitamins

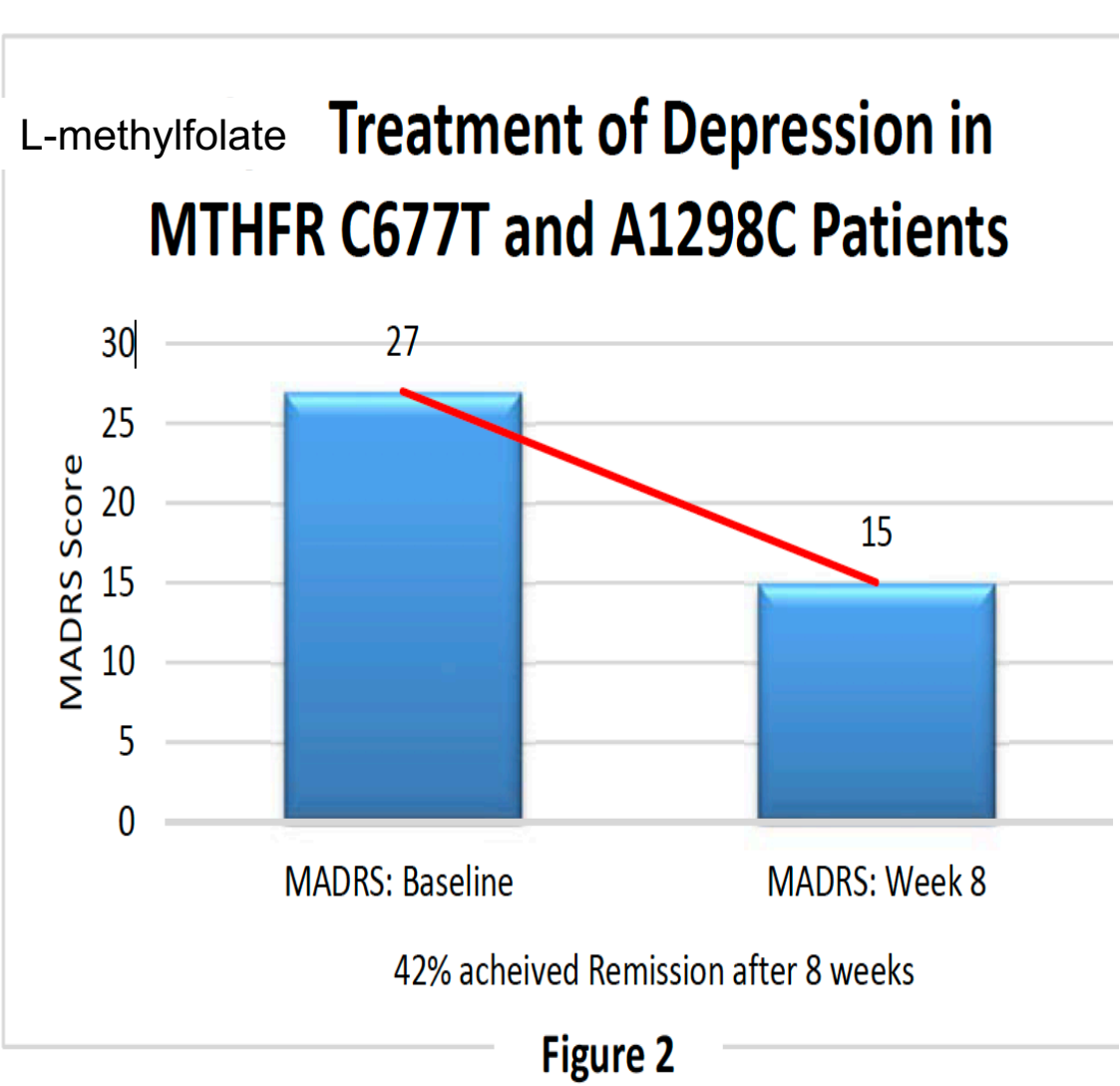


Figure 55: L-methylfolate (Papakostas, 2014)

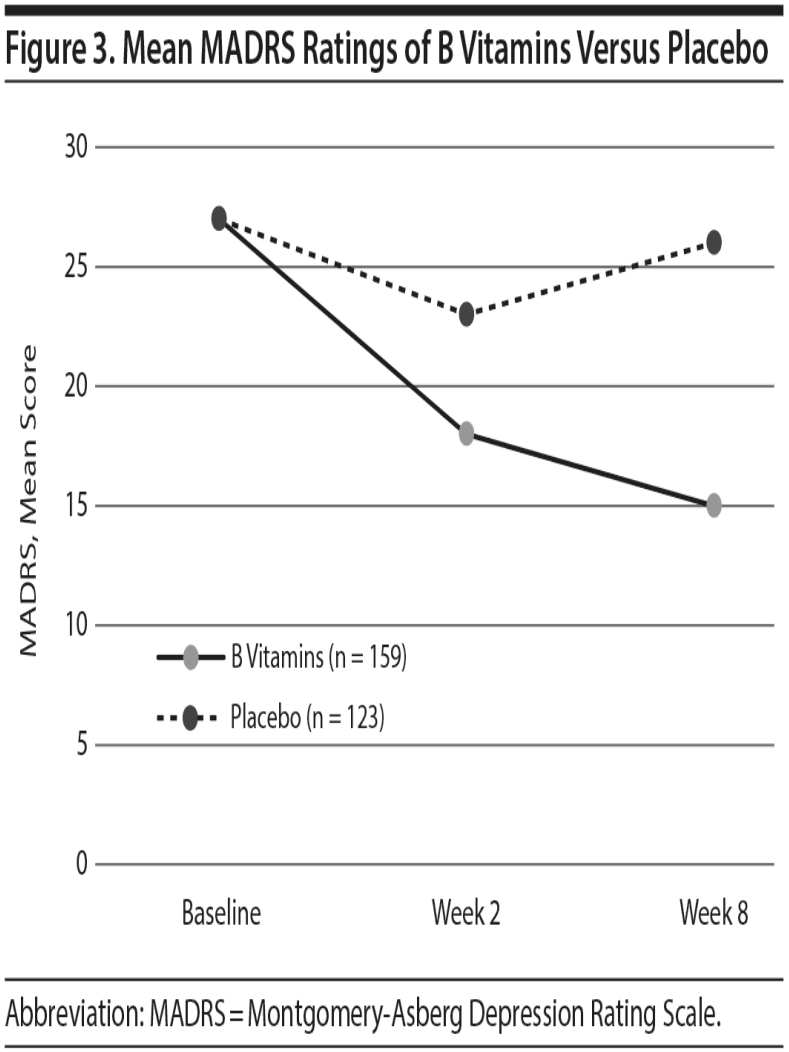


Figure 54: Mean MADRS (Mech & Farah, 2016)

(Papakostas., 2014) (Merch & Farah, n.d.)

CACNA1C

Total gray matter was highest in AA carriers of the risk SNP (rs1006737) compared to GA and GA carriers.

The CACNA1C risk variant for Bipolar Disorder (BD) consists of the presence of the A allele

A/A genotype has been associated with greater CACNA1C messenger RNA expression in the Prefrontal cortex compared with G/G or A/G genotypes.[27]

(Bigos et al., 2010) & (Soeiro-de-Souza et al., 2017)

ANK3

ANK3

- C / C — The initial characterization of Ank3 C/C
- C / T — We have found that *Ank3 C*/T mice with one functional copy exhibit altered mood-related behaviors, hyperactive impulsivity, and elevated stress reactivity, without any detectable motor deficits as in null Ank3 T/T mice
- T / T — The initial characterization of Ank3 T/T mice that completely lack brain-specific isoforms noted a progressive early-onset ataxia due to impaired action potential firing at axon initial segments (AIS) of Purkinje neurons in the cerebellum, which is important for motor control

(Leussis, Madison, & Petryshen, 2012)

MC4R – SNP rs489693

C / C One common variant of the MC4R gene, carried by 22% of the general population, causes reduced MC4R protein level in the hypothalamus of the brain. Carriers of this variant have both increased appetite and decreased satiety. They tend to eat larger amounts of food, snack more frequently, and like to eat fatty foods. Studies have shown that each copy of the variant is responsible for a BMI (Body Mass Index) increase of 0.22 and an obesity risk increase of 8%.

C / A Medium risk of antipsychotic-induced weight gain

A / A High risk of antipsychotic-induced weight gain

MC4R gene mutations are associated with dominantly inherited **obesity** in man Approximately **4% of early-onset obesity** is attributed to **heterozygous mutations** of the MC4R gene. Carriers of MC4R mutations are hyperphagic, hyperinsulinemic, have higher bone mineral density, and have more rapid linear growth than matched control subjects. (Martin, White, Kammerer, & Witchel, 2002)

(GBHealthWatch, n.d.)

MC4R-antipsychotic weight gain

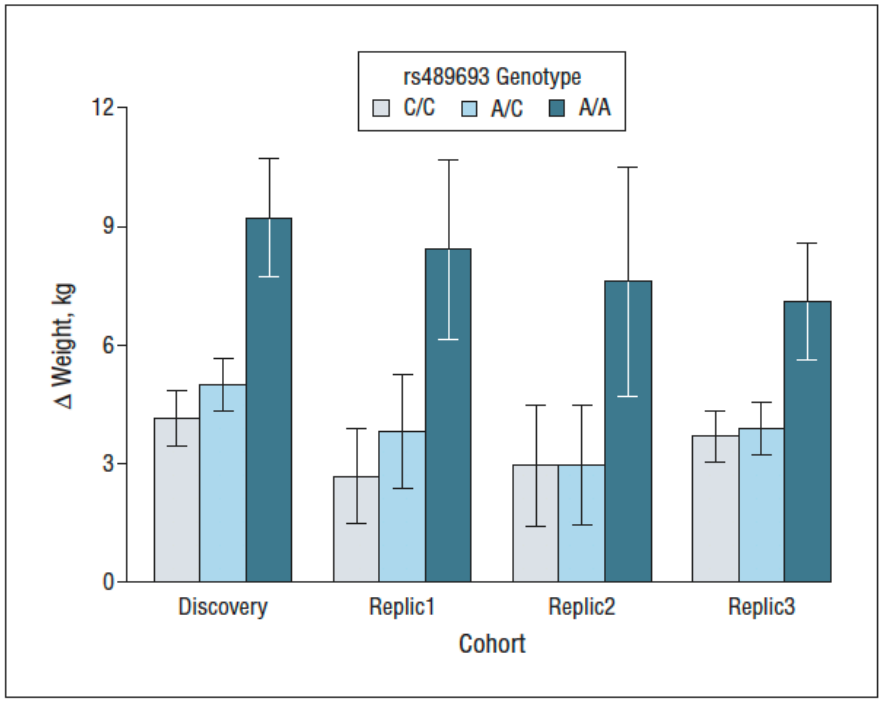


Figure 3. Single-nucleotide polymorphism rs489693 genotype and antipsychotic drug–induced weight gain in 4 cohorts of subjects. Replic1 indicates the first replication cohort; Replic2, the second replication cohort; Recplic3, the third replication cohort.

Figure 59: Rs489693 (Malhotra et al., 2012)

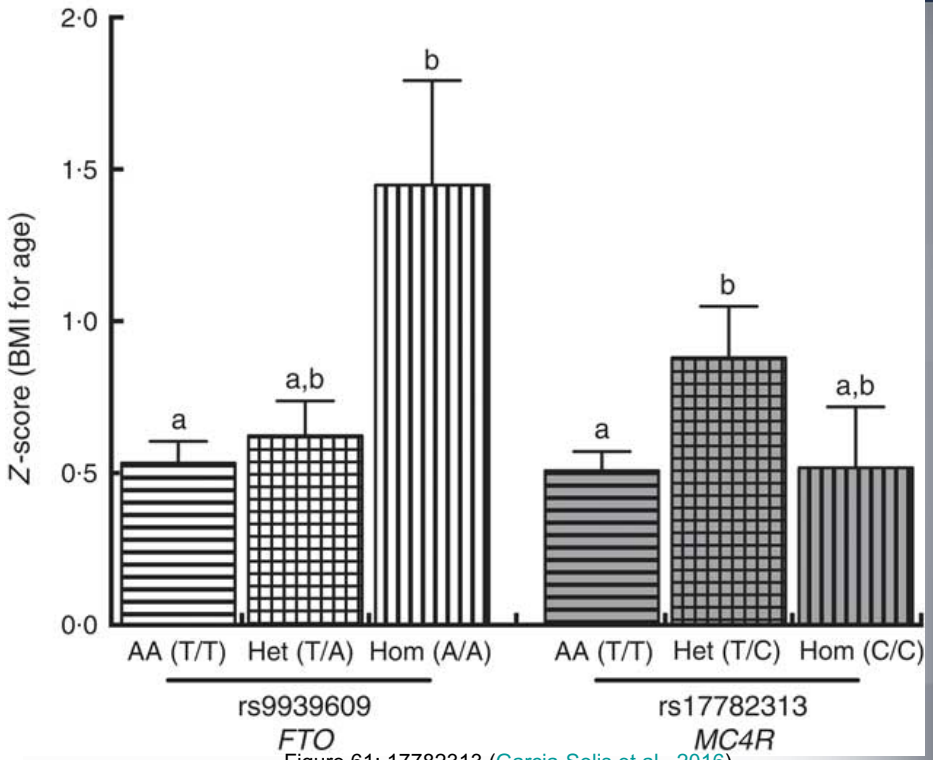


Figure 61: 17782313 (Garcia-Solis et al., 2016)

Comparison between BMI-for-age *Z*-score and *FTO* and *MC4R* rs11782313 genotypes.

(Malhotra et al., 2012) (Garcia-Solis et al., 2016)

MC4R: Personal Experience

- Weight Loss Meds
  - Lorcaserin (5HT2C agonist)
  - Orlistat
  - Amphetamine
  - Methylphenidate
  - GLP-1 agonists
  - Buproprion/naltrexone
  - Inositol
  - Topiramate
  - CBD

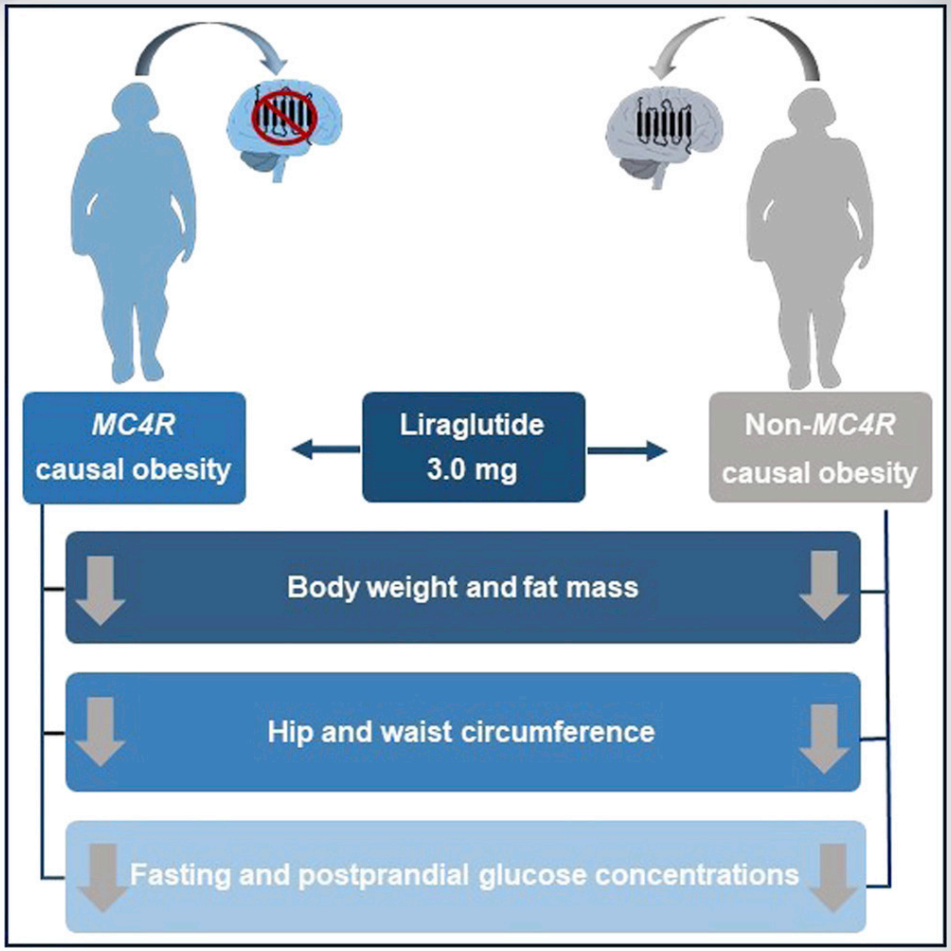
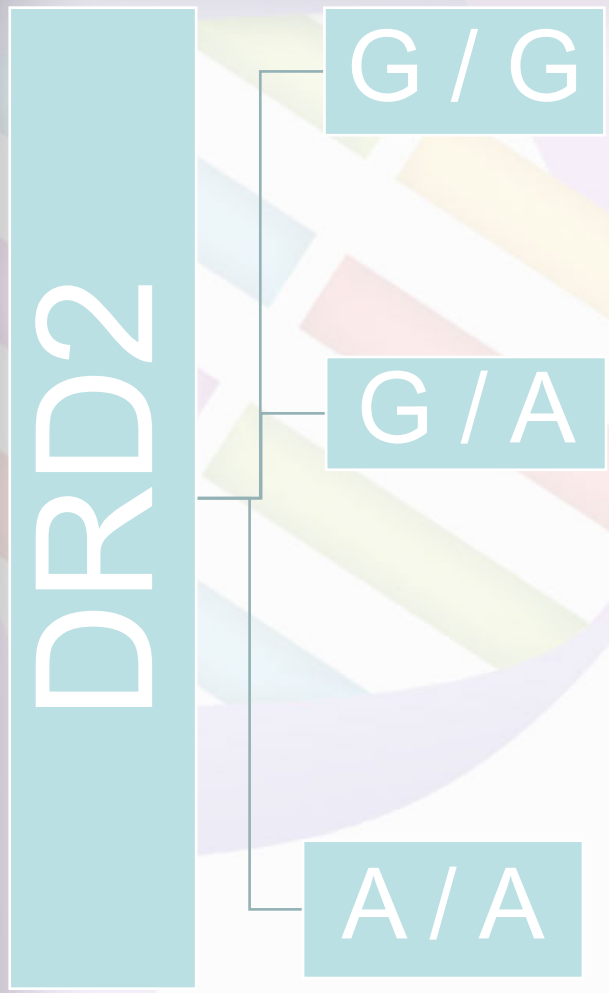


Figure 63: MC4R and GLP-1 (Iepsen et al., 2018

(Ipsen et al., 2018)

DRD2-SNP rs1799732



The Major "G" allele is associated with:

•Decreased effect of NRT tobacco dependence drug therapy in tobacco dependent patients

•Increased effect of bupropion tobacco dependence drug therapy in tobacco dependent patients

•More favorable treatment outcome of schizophrenia

The Minor "A (DEL)" allele is associated with:

•Younger onset schizophrenia

•Less favorable treatment outcome for schizophrenia

•Increased risk of inhaling heroin abuse

•Boys with multiple polymorphisms in the DRD2 gene demonstrate higher reward-dependence and novelty seeking

•Increased effect of NRT tobacco dependence drug therapy Decreased effect of bupropion tobacco dependence drug therapy in tobacco dependent patients

•AA= increased risk of severe alcoholism (2.0 times

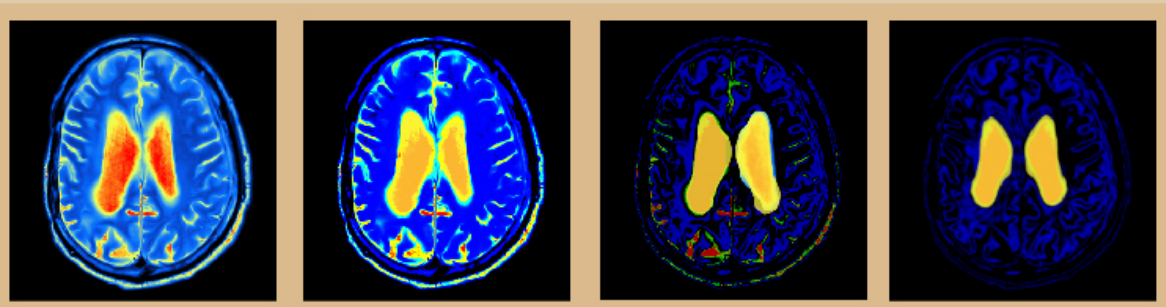
(GeneCards, n.d.)

DRD2

D2 Receptors + Anhedonia

Versus controls, addicted subjects were found to have lower D2 receptor (D2R) expression and lower baseline dopamine release

- These changes cause a blunted response to natural rewards such as food and sex
- Drug-induced dopamine overcomes baseline deficiencies



Normal Brain | *Brain of an obese person* | *Brain of a cocaine user* | *Brain of an alcoholic*

Red = high D2R expression

DRJOCKERS.COM

Figure 64: D2 (Jockers, n.d.)

(Dr. Jockers, n.d.)

COMT-SNP rs4860

Val / Val
G/G

Val / Met
G/A

Met / Met
A/A

- Higher activity levels of COMT protein, lower dopamine levels in the prefrontal cortex (brain) (GG)

- Lower activity levels of COMT protein, higher dopamine levels in the prefrontal cortex (brain) (AA)

(selfdecode, n.d.)

COMT-SNP rs4860

MET allele positives

- **More Creative**
- **Higher IQ** (tested in people with schizophrenia).
- **Better working memory.**
- **Better verbal working memory**(letter-number sequencing)
- Better reading comprehension
- More **plasticity** in older age
- **More Exploratory**
- Increased verbal fluency for males (but decreased it for females).
- Met/Met's get **more pleasure** out of life **but also more misery** (bigger high's and low's).

MET allele negatives

- Issues with methylation and not breaking down estrogen byproducts (catechol estrogens). **Higher homocysteine.**
- **Anxiety**: OCD, panic disorder, phobic anxiety, more neurotic, more impulsive/compulsive, depression, **"ADHD"** (**My opinion ODD**)
- Increased aggression
- Fibromyalgia
- Impairment in emotional reactivity female (but not male) mice
- **(Met) allele** frequency **higher among alcoholics**
- low cognitive flexibility.

VAL allele positives

- Better handling of stress and pain.
- Better at learning languages.
- More Cooperative, Helpful and Empathic (GG, in females)
- **Higher emotional resilience**
- **Increased verbal fluency for females** (also decreased for males).
- More easily hypnotized
- **More methylation in the gut**
- **Responded well to modafinil**
- **More Extroverted**

VAL allele negatives

- **Less pleasure out of life**
- **Lower IQ**
- Worse executive function
- Worse fine motor skills
- Less Exploratory
- More **childhood depressive symptoms**
- 2X Increased risk for **breast cancer**.
- Increased risk for **endometrial cancer**.
- Egan et al. (2001) concluded that the **COMT val allele**, because it increases prefrontal dopamine catabolism, **increases risk for schizophrenia.**

(selfdecode n.d.)

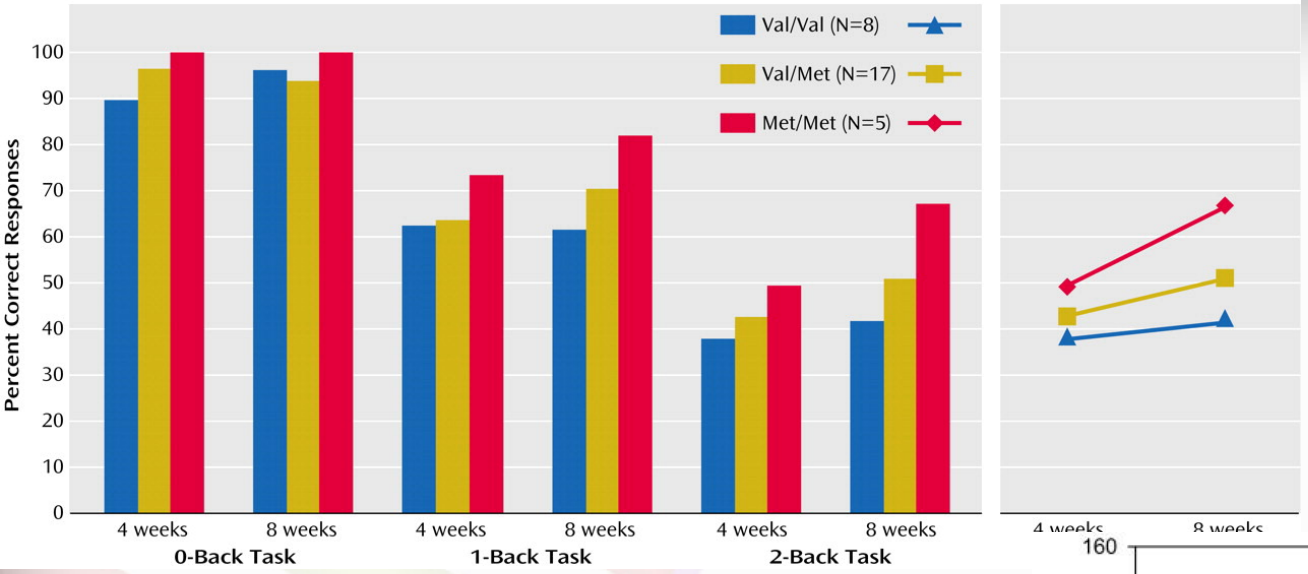
COMT-SNP rs4860
MID COMT, MID Dopamine (G/A = VAL /Met)

COMT VAL/MET

- **Pleasure out of life** - AA's had twice the positive emotion towards a pleasant event than GG's. GG people subjectively viewed a very pleasurable event on the same level that AA would view a slightly pleasurable event. AG had a mid-level. The effect for this was "quite large".
- **Cognitive function when not under stress:** A/A has better attention and processing of information (executive function). However, realize that this one gene only accounts for 4% of the difference in executive function. The FAB exam tests executive function. GG scored an average of 16.0, GA 15.7 and AA 15.3. These scores are statistically significant, but not large.

(selfdecode, n.d.)

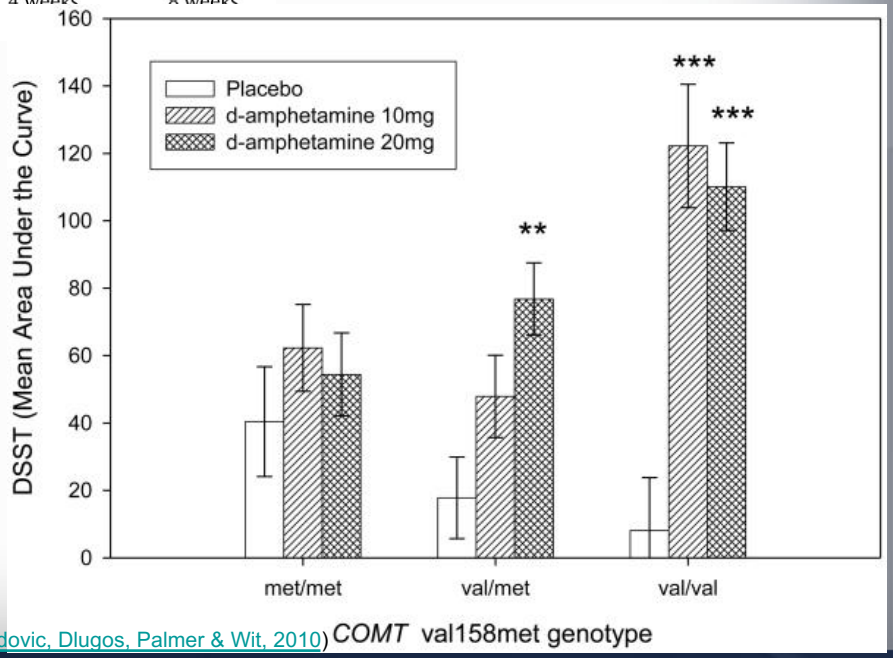
COMT Variant Response to Atypical Antipsychotics and Amphetamines



COMT MET/MET = Improved response **antipsychotics**

Figure 66: Atypical Response (Bertolino et al., 2004)

COMT **VAL/VAL** = Improved response **amphetamines**



(Hamidovic, Dlugos, Palmer, & Wit, 2010)
(Bertolino et al., 2004)

Figure 67: Amphetamine COMT (Hamidovic, Dlugos, Palmer & Wit, 2010)

ADRA2 SNP- rs1800544

ADRA2A

- C / C
- G / C
- G / G

ADRA2A- Alpha-2A Adrenergic Receptor

- This gene codes for the ADRA2A which binds pre-synaptically norepinephrine in the prefrontal cortex
- Receptor involved in neurotransmitter release
- 1291G>C
  - C/C Reduce response to Methylphenidate
  - G alleles carriers had greater improvement of inattentive symptoms with Methylphenidate treatment compared with C-allele

(1. Polanczyk G et al., Arch Gen Psychiatry, 2007
2. da silva TL et al, Journal of neural transmission, 2008)

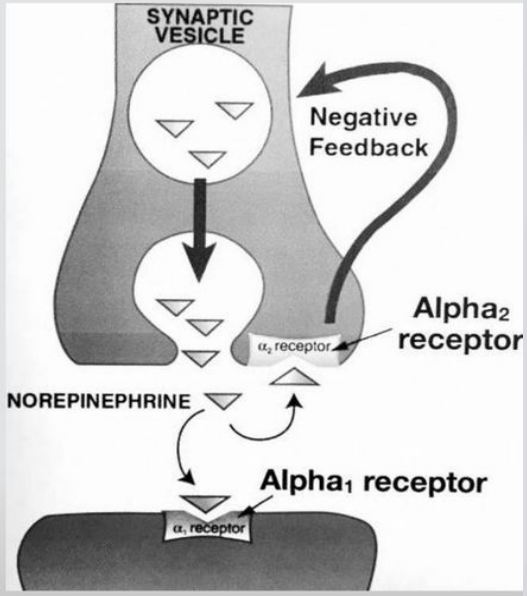
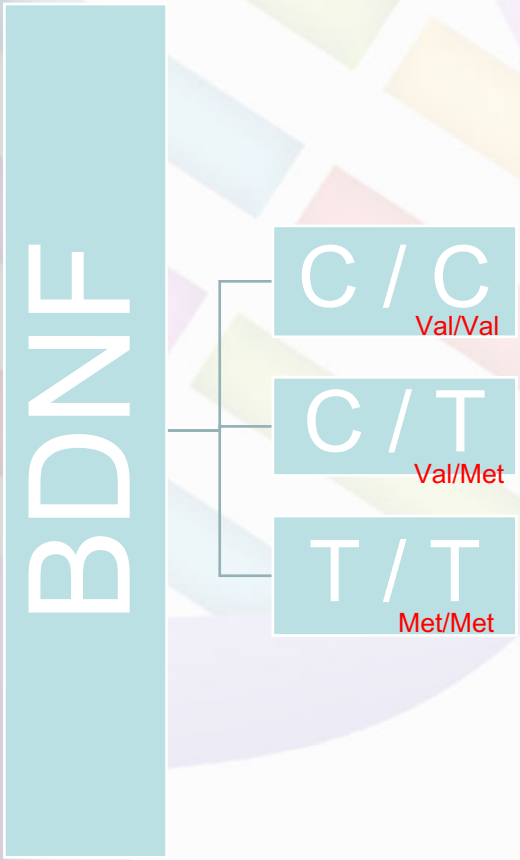


Figure 69: ADRA2A (Namerow, 2018)

- **The G (minor) allele is associated with:**
- Increased consumption of sweet food products (GG).
- Increased scores in **depression** assessments (GG).
- **Lower morality** scores in GG subjects.
- Increased **inattention** in GG subjects.

(Namerow, 2018)

BDNF-SNP 6265



The difference between CT and CC was negligible. BDNF may exert its observed effects on N-acetyl-aspartate via its influence on the glutamate system

Significantly lower N-acetyl-aspartate and Glutamate metabolic ratios compared with CC. The T allele is associated with abnormal packaging of the precursor of BDNF and decreased mature BDNF production in cells

(Genecards, n.d.) & (Uniprot, n.d.)

BDNF-SNP 6265
T allele associated with abnormal packaging of BDNF

T allele positives	T allele negatives	C allele positives	C allele negatives
• Lower BMI (T/T) • Lower sys BP • Lower neurodegeneration • Lower Depression incidence when subject to defeat • Normal level sexual desire compared to c/c • Preserved gray matter in MS • Increased positive attitude and reduced desire to stop once exercising • Reduced HPA axis/stress response to psychosocial stressors • 21% protective effect in substance related disorders	• Decrease hippocampal vol. • More anxiety (T/T) • Impaired motor skills • Introversion –higher prevalence of Ts in Asians • Impaired learning and memory • Increased likelihood of car accidents • Lengthened recovery time for stroke • Increased binges after restriction • 33% chance increased risk of eating disorders • increased risk schizophrenia • Poorer executive functioning OCD • Higher Alzheimer's risk in non-APOE4 carriers • Increased risk suicidal behaviors • Higher risk alcohol-related depression • Sensitivity childhood adversity	• 20 min. more slow-wave sleep • Double EEG alpha waves (both rested and sleep deprived states) • Better accuracy verbal working memory • Higher performance in digital working memory and spatial localization in Chinese • Higher mean intelligence • Better response to TMS with drug-resistant depression • Reduced stress-induced anxiety-like behavior • Women less likely to be overweight than people with T allele	• Stronger reaction to negative emotions (e.g., angry, fearful, and sad faces) • Higher risk for allergies. • Increased levels of BDNF in blood, lung fluid, and nose fluid positively correlate with disease activity. • ADHD while CT is associated with ADHD with intellectual disability • Twice the risk of being an overweight male • Depression in individuals with higher levels of cortisol in CC but not in CT

(selfdecode n.d.)

BDNF

(tmedweb, n.d.)

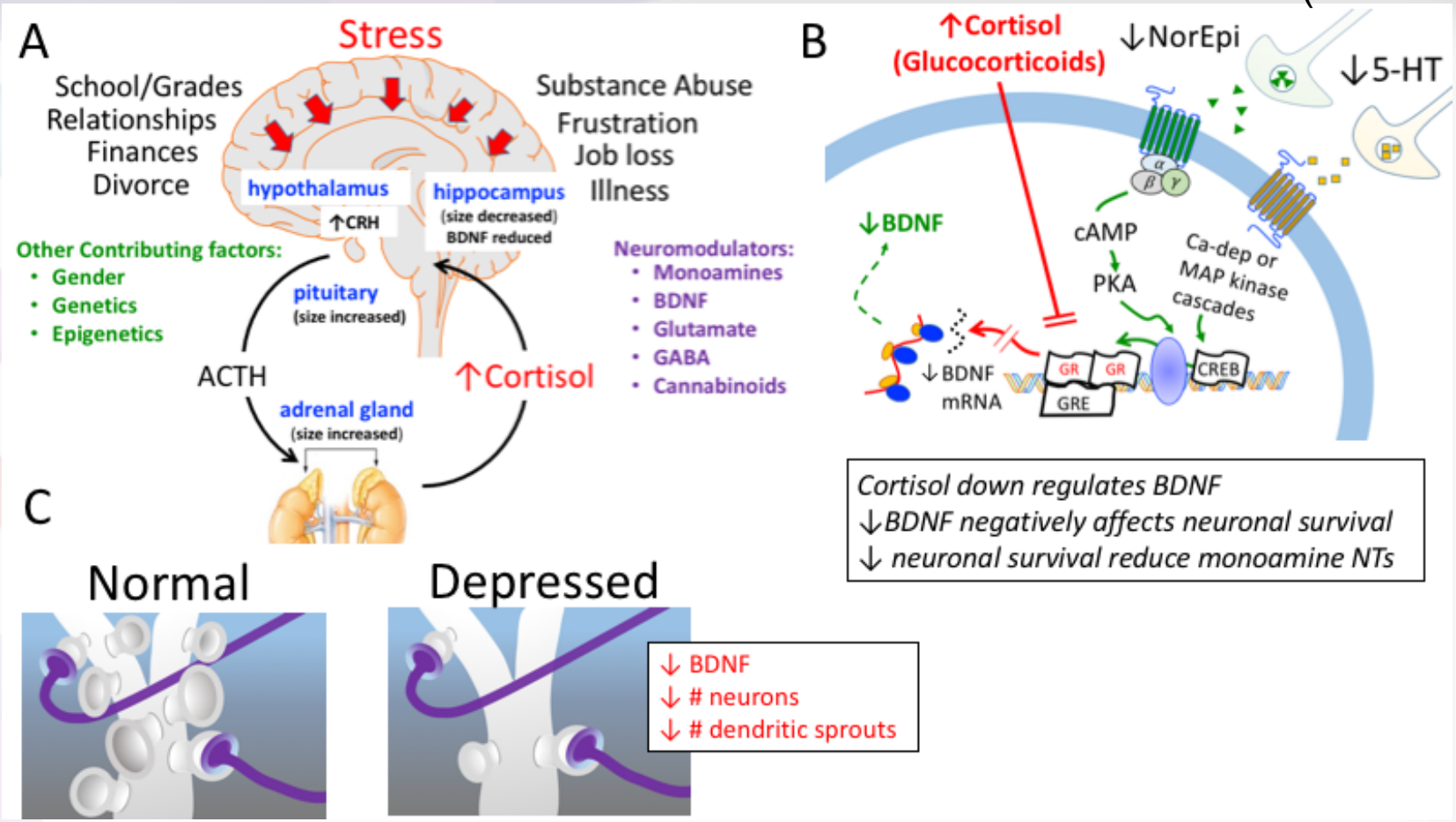


Figure 1. The neurotrophic (stress) hypothesis of depression. **Panel A:** A combination of stress, genetics and environmental factors result in increased activation of the hypothalamic-pituitary axis, and chronic elevations in cortisol. **Panel B:** Chronic elevations of cortisol down-regulate the expression of multiple glucocorticoid-sensitive genes, including BDNF. **Panel C:** Reductions in BDNF result in neuronal atrophy and decreased synaptic density (Duman & Aghajanian, 2012). Decreased BDNF levels and increased cortisol levels are believed to cause the reduced size of the hippocampus (a brain region involved in memory & mood control) and increased size of the pituitary and adrenal glands (Sapolsky, 2000; Belmaker & Agam, 2008). BDNF: Brain-derived neurotrophic factor.

Figure 71: BDNF Cortisol (Tulane Pharmwiki, n.d.)

BDNF

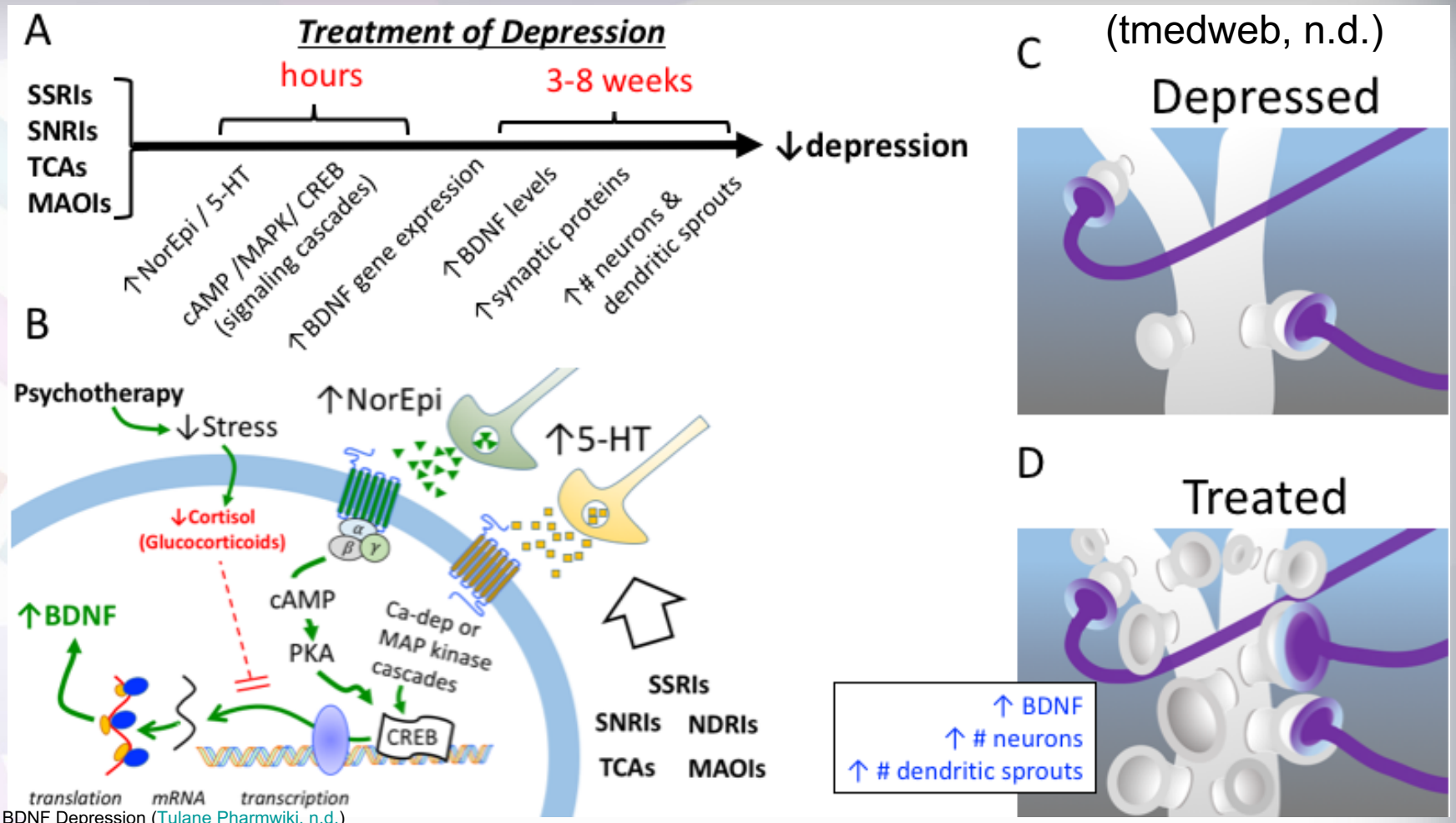


Figure 72: BDNF Depression (Tulane Pharmwiki, n.d.)

Figure 2. Neurotrophic hypothesis for antidepressant action. **Panel A**: Timeline of events involved in mediating a therapeutic response to antidepressant therapy. Antidepressants rapidly elevate synaptic levels of monoamines. Over several weeks, an upregulation in the expression of BDNF produces an increased growth of neurons and upregulation of biochemical pathways involved synaptic transmission, resulting in a reversal of depressive symptoms. **Panel B:** Antidepressants produce a rapid increase in synaptic levels of serotonin & norepinephrine, which stimulate cAMP response element-binding protein (CREB) through different converging signal transduction pathways. CREB stimulation upregulates the expression of BDNF which causes increased neuronal growth and plasticity (as illustrated in **Panels C & D**). Psychotherapy may produce similar &/or complementary effects by stress reduction, which can reduce cortisol levels.

BDNF – increased by Ketamine

(tmedweb, n.d.)

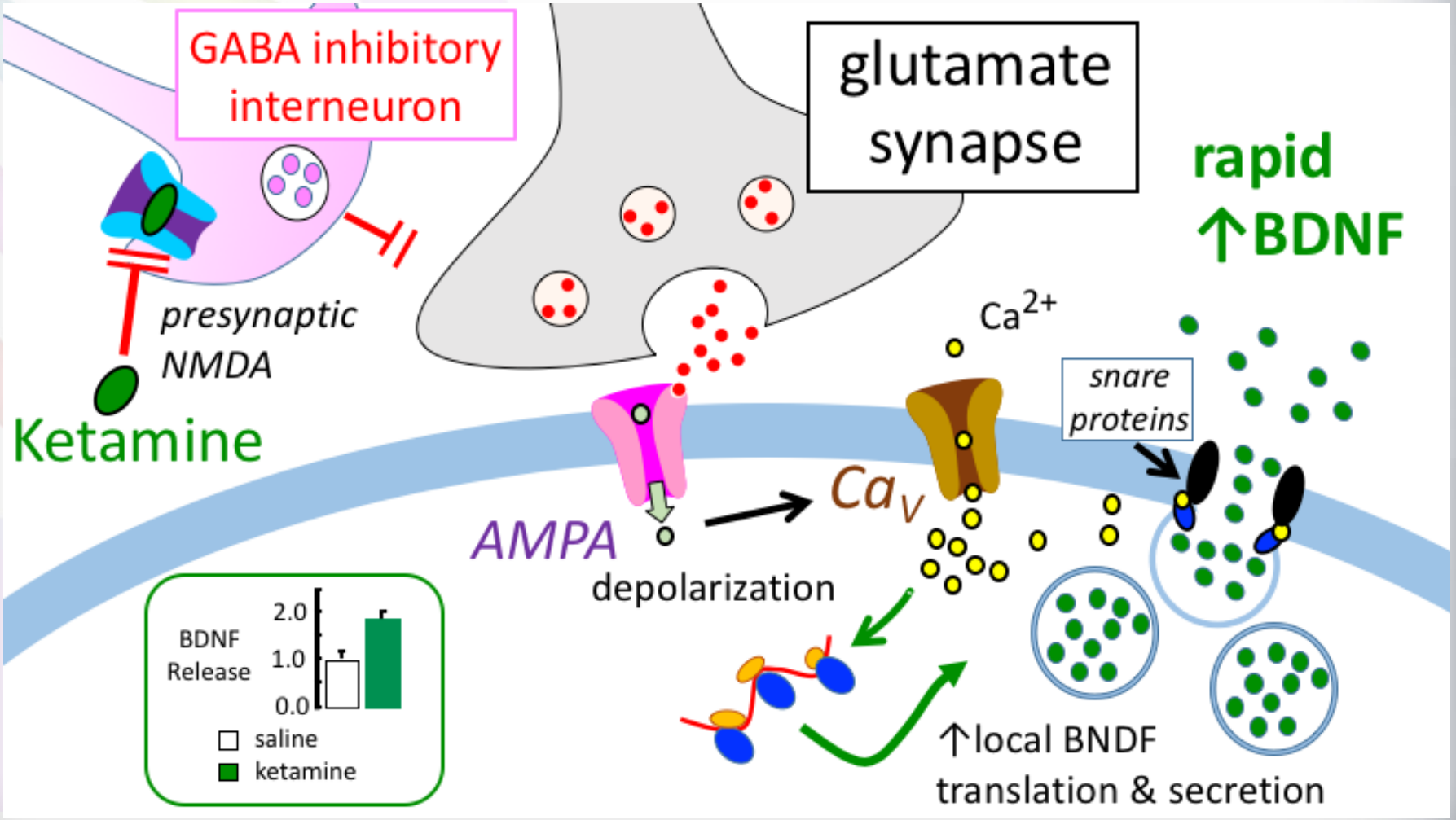
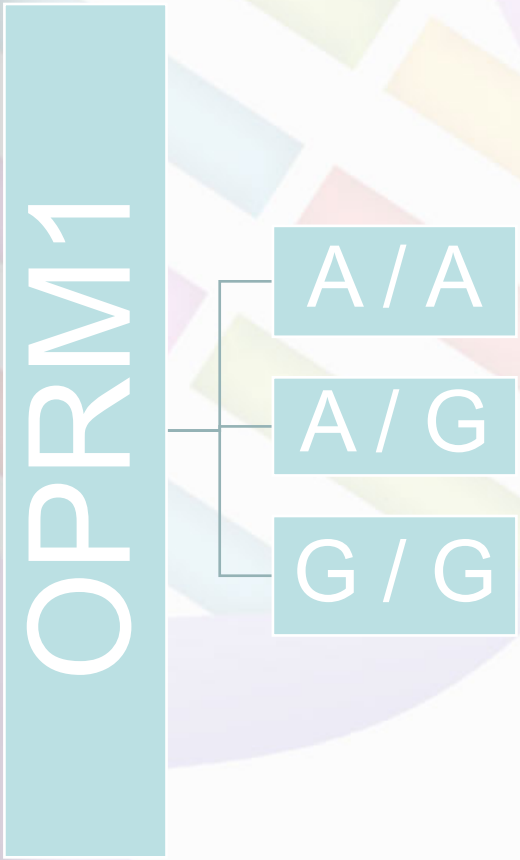


Figure 73: BDNF GABA (Tulane Pharmwiki, n.d.)

OPRM1



Altogether, the *OPRM1* 118A>G SNP affects mechanisms related to individual sensitivity to pain, opioid efficacy, and opioid-related side effects, tolerance, dependence and reward. Particularly, carriers of the **118G allele** should **require increased μ-opioid drug doses** in order to get analgesic effects, and once the analgesic effect is reached, they should show opioid-related side effects. Patients carrying the 118G allele may show either an unaltered or a higher sensitivity to pain compared with patients homozygous for the 118A allele, depending upon the individual endogenous opioid tone. In fact, the **118G allele** has been **associated** both to **low levels of μ-opioid receptors** and to **increased sensitivity to endogenous opioids**. It has thus been related to two effects that may compensate each other.

(Mura et al., 2013)

OPRM1-SNP rs1799732
G allele decreases opioid receptors

(selfdecode n.d.)

OPRM1-SNP rs1799732
G allele decreases opioid receptors

Bad

- Higher Neuroticism scores
- Vulnerable to stress and depression
- Feels more pain from social rejection
- Decreased opioid receptors a lower available receptors to bind with drugs possibly triggering opioid addiction
- Less positive effects from placebo
- Opioids don't work as well for pain
- Greater increase in urge to smoke after high dose alcohol

Good

- Less submissive behavior
- Resilience to social defeat
- Reductions in anhedonia
- Increased tendency to engage in affectionate relationships
- Experience more pleasure in social situations
- Lower risk of obesity
- Women more successful with speed dating
- Low dose naltrexone may be helpful?

(selfdecode n.d.)

GRIK1-SNP rs2832407

Results from studies have shown that for every 2-3 people with the GRIK1 C/C genotype who were treated with topiramate, one will respond vs. one in every 322 people with an A- allele who will respond (Feinn et al., 2016).

The rs2832407(C) allele has inconsistently been linked to alcoholism and its treatment. Nonetheless, a 2014 report based on 138 patients concludes that rs2832407(C;C) individuals show a greater decrease than non-carriers (of a rs2832407(C) allele) in the number of heavy drinking days per week when taking topiramate at a dose of 200 mg/daily. [PMID 24525690]

A follow-up study done 3 and 6 months after treatment seemed to mostly confirm the topiramate benefit preferentially to rs2832407(C;C) individuals [R].

(selfdecode n.d.)

GRIK1-SNP rs2832407

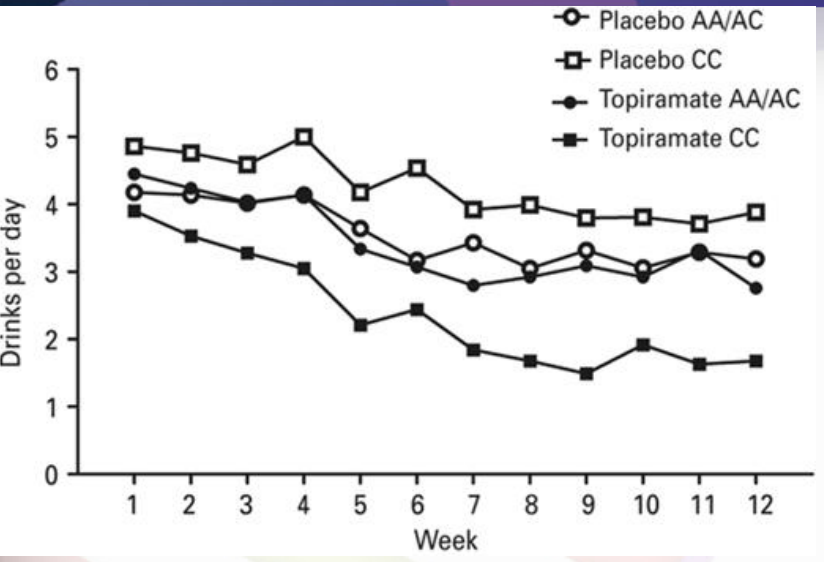


Figure 77: GRIk1 Topamax (Kranzler, Richard, Tennen, Gelernter, & Covault, 2014)

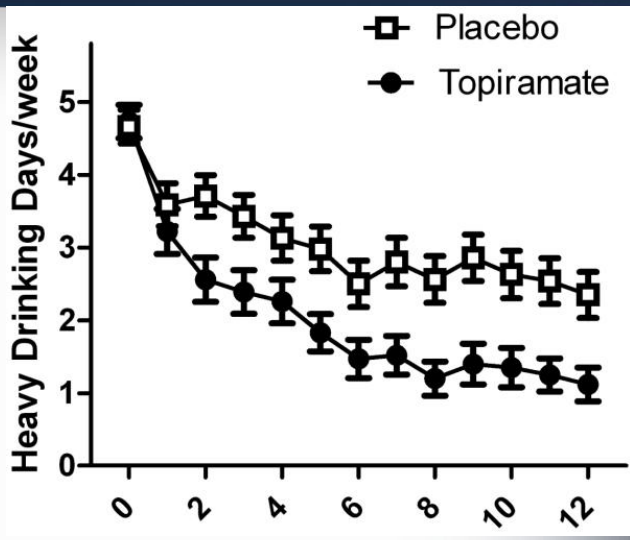


Figure 78: GRIk1 Topirimate (Kranzler, Richard, Tennen, Gelernter, & Covault, 2014)

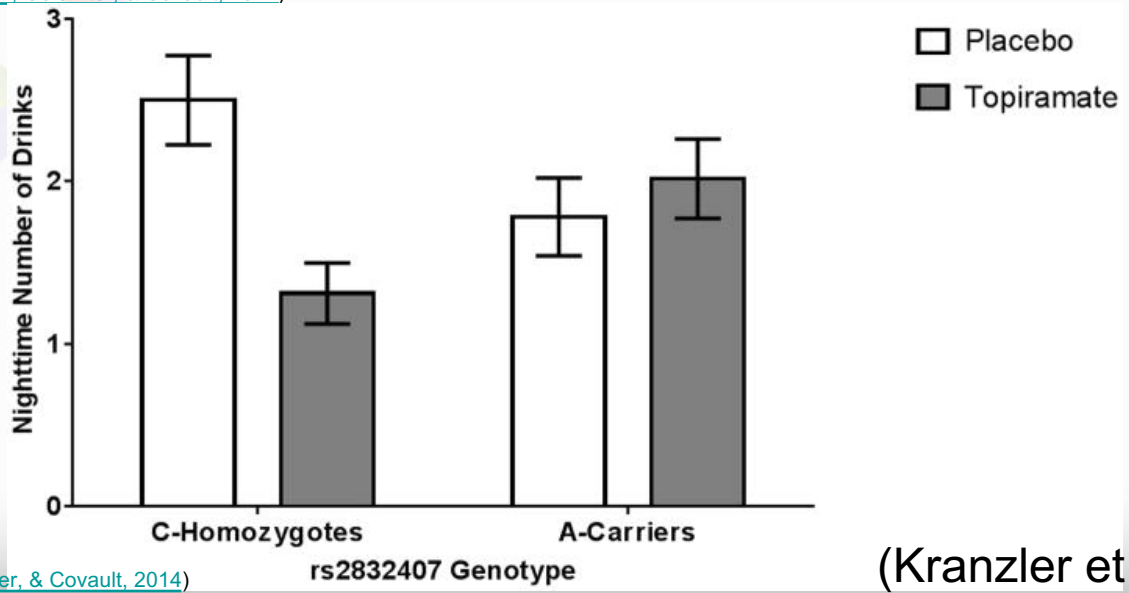


Figure 79: rs2832407 (Kranzler, Richard, Tennen, Gelernter, & Covault, 2014)

(Kranzler et al., 2014)

Pharmacokinetics

Before discussing pharmacodynamics in PREV , it is important to define the term and distinguish this branch of pharmacology from the branch called pharmacokinetics.

Pharmacokinetics is the branch of pharmacology that studies the relationship between time and the concentration of a drug at various sites in the body, by measuring the absorption, distribution, metabolism, and excretion of the drug.

Pharmacodynamics, on the other hand, studies the effects of a drug on the body by measuring drug binding to receptors and dose-response curves.

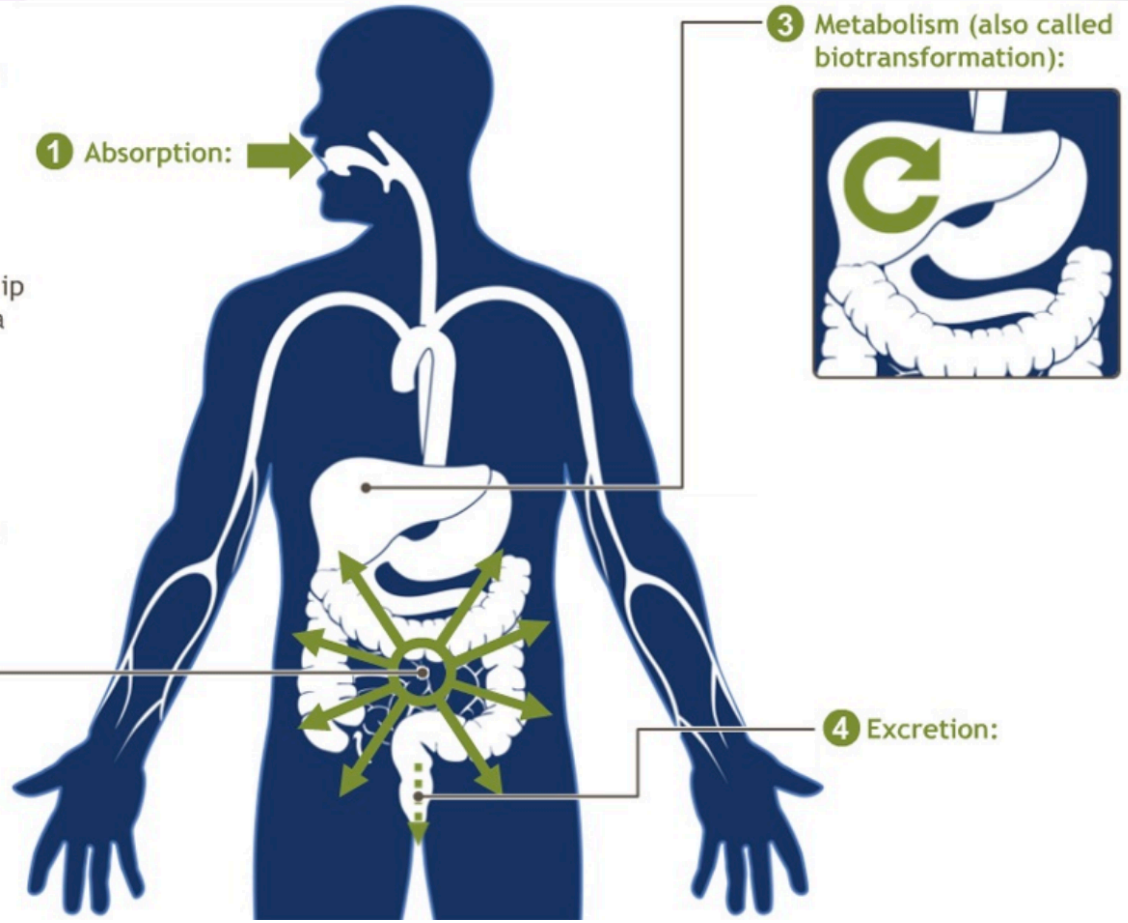


Figure 84: Pharmacodynamic4 (Adamondemand, n.d.)

(adamondemand, n.d.)

Pharmacokinetics: Types of Metabolizers

Metabolizer Phenotype	Description	Effect
Poor Metabolizer (PM)	Patients with little to no functional metabolic activity.	Enzymes break down Standard drugs very slowly, creating risk of toxicity because drug is slow to be eliminated. Pro-drugs are less effective because they are activated more slowly.
Intermediate Metabolizer (IM)	Patients with reduced metabolic activity.	At approved doses, enzymes will be slightly slower in breaking down Standard drugs, requiring a slightly lower dose to avoid toxicity. Pro-drugs may be less effective because of slower metabolism.
Normal Metabolizer (NM)	Patients with normal metabolic activity.	Produces desired outcome as expected when dosed according to FDA approved labels.
Rapid Metabolizer (RM) or Ultrarapid Metabolizer (URM)	Patients with substantially increased metabolic activity.	Enzymes break down and eliminate drugs very quickly, often reducing the effectiveness of the drug. Standard doses may not be sufficient to produce the desired result. Pro-drugs are activated more quickly, creating risk for toxicity.

Figure 86: Drug Metabolism (Personalized Health Solution, n.d.)

Genes to Cover

- CYP1A2
- CYP2B6
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4/5

Pharmacokinetics: Types of Metabolizers Examples

CYP1A2
- asenapine
- Clozapine
- fluvoxamine

CYP2B6
- buproprion
- sertraline

CYP2D6
- aripiprazole
- brexpiprazole
- Vortioxetine
- amphetamine

CYP2C9
- Fluoxetine
- Valproic acid

CYP2C19
- diazepam
- Citalopram
- escitalopram

CYP3A4/3A5
- cariprazine
- Lurisadone
- Quietiapine
- Alprazolam

Figure 86: Drug Metabolism (Personalized Health Solution, n.d.)

Factors Influencing CYP

Ethnicity	CYP2D6		CYP3A4		CYP1A2	
	PM	UM	PM	UM	PM	UM
Caucasian	8%[33,34]	1%–10%[163]	2%–9.6%[164]	14%[162]	NSD	NSD
African	3%–8%[33,34]	2%–29%[165]	26%–67%[164]	67%[162]	NSD	NSD
Asian	6%–10%[33,34]	0%–2%	0%–22%[164]	NSD	5%[166]	NSD
Japanese	0.39%[35]	NSD	NSD	NSD	14%[166]	NSD
Korean	0.22%[36]	NSD	NSD	NSD	NSD	NSD
Australian	NSD	NSD	NSD	NSD	5%[7]	NSD

Abbreviations: PM, poor metabolizers; UM, ultrafast metabolizers; NSD, no study done.

Figure 95: Ethnicity and cytochrome (Researchgate, n.d.)

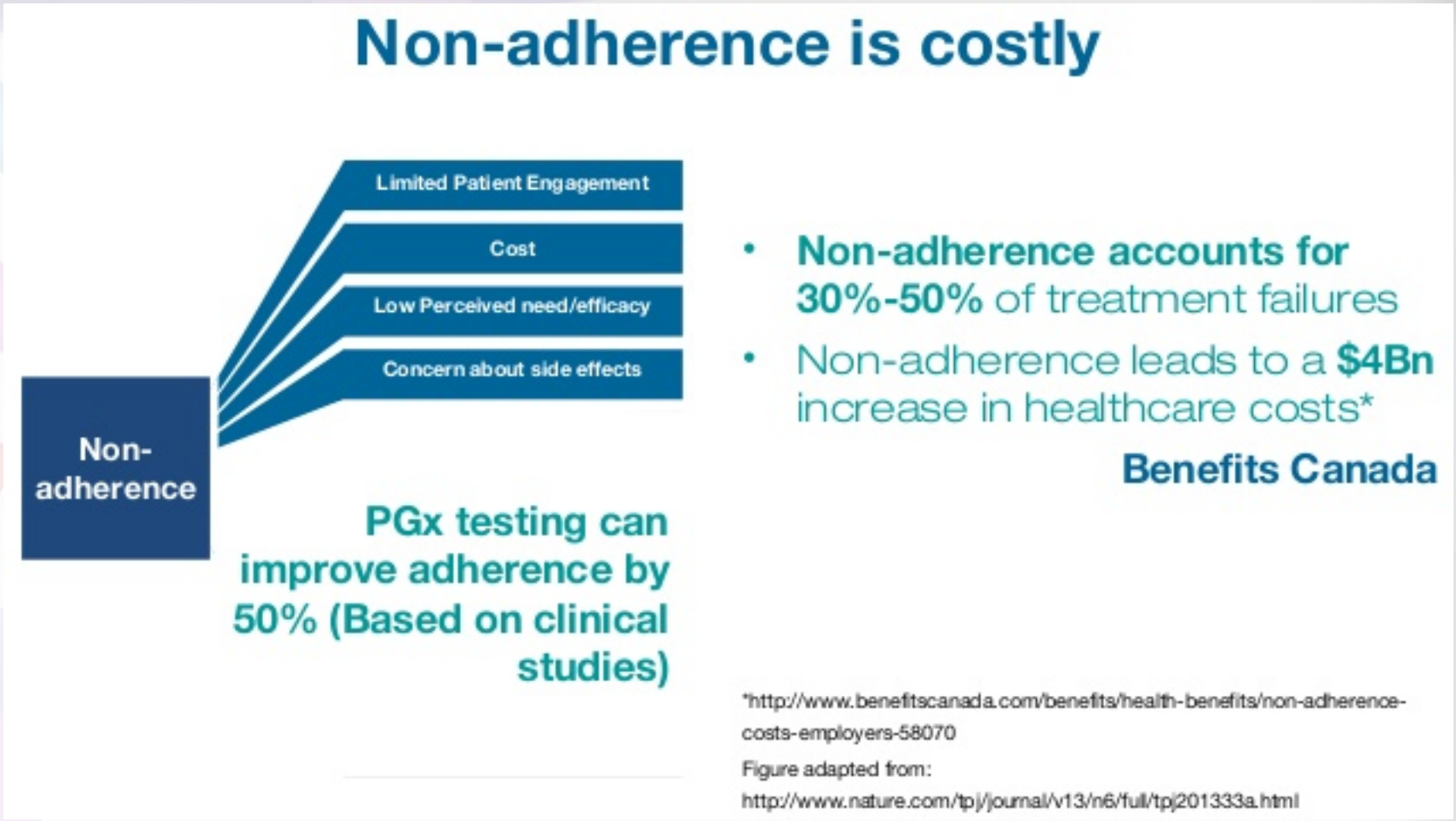
Nutrition	**1A1;1A2; 1B1, 2A6, 2B6, 2C8,9,19; 2D6, 3A4,5**
Smoking	**1A1;1A2, 2E1**
Alcohol	**2E1**
Drugs	**1A1,1A2; 2A6; 2B6; 2C; 2D6; 3A3, 3A4,5**
Environment	**1A1,1A2; 2A6; 1B; 2E1; 3A3, 3A4,5**
Genetic Polymorphism	**2A6; 2C9,19; 2D6;**

Figure 94: CYP Nutrition (Dumontier, 2010

Red indicates enzymes important in drug metabolism

(Dumontier, 2010)
(researchgate, n.d.)

Financials and Personalized Medicine

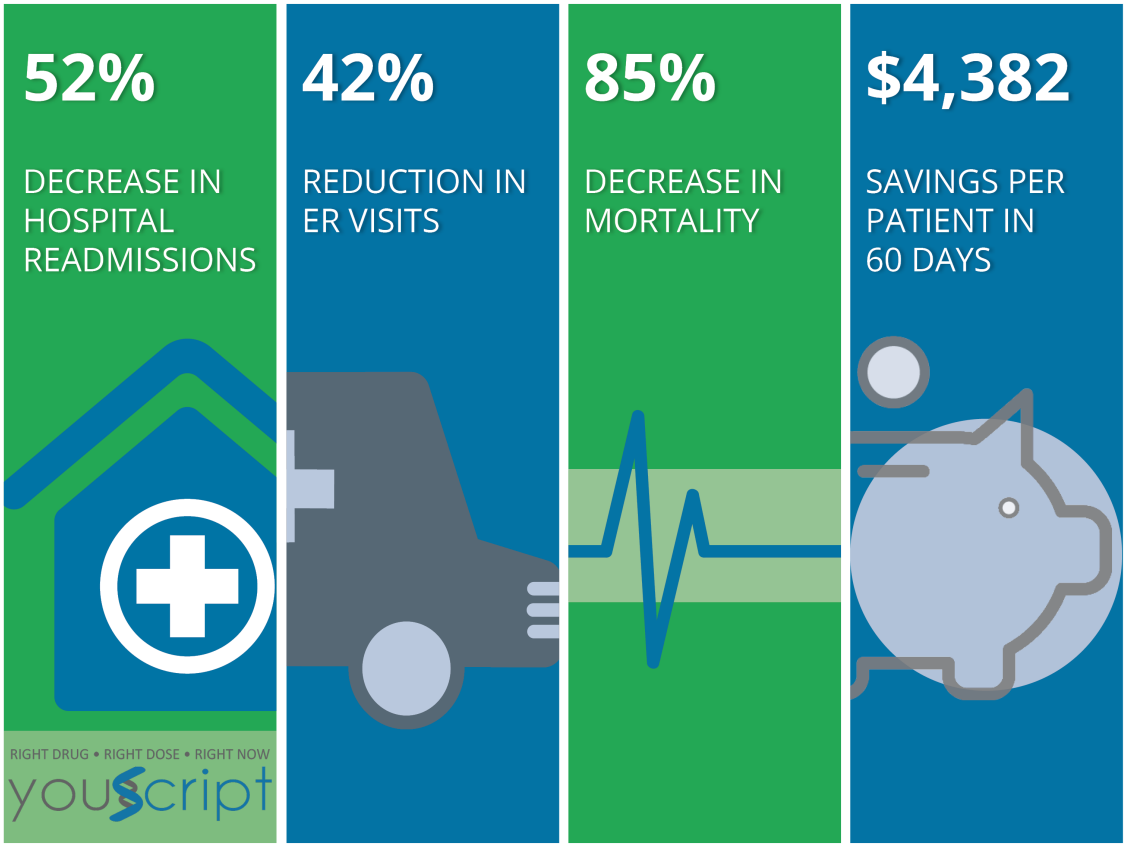


- Figure 98: Non-adherence (Medavie Blue Cross, 2017)

(Medavie Blue Cross, 2017)

Financials and Personalized Medicine

Genetic testing resulted in:



- Figure 97: New Precision Medicine (YouScript, n.d.

(Youscript, n.d.)

Financials and Personalized Medicine

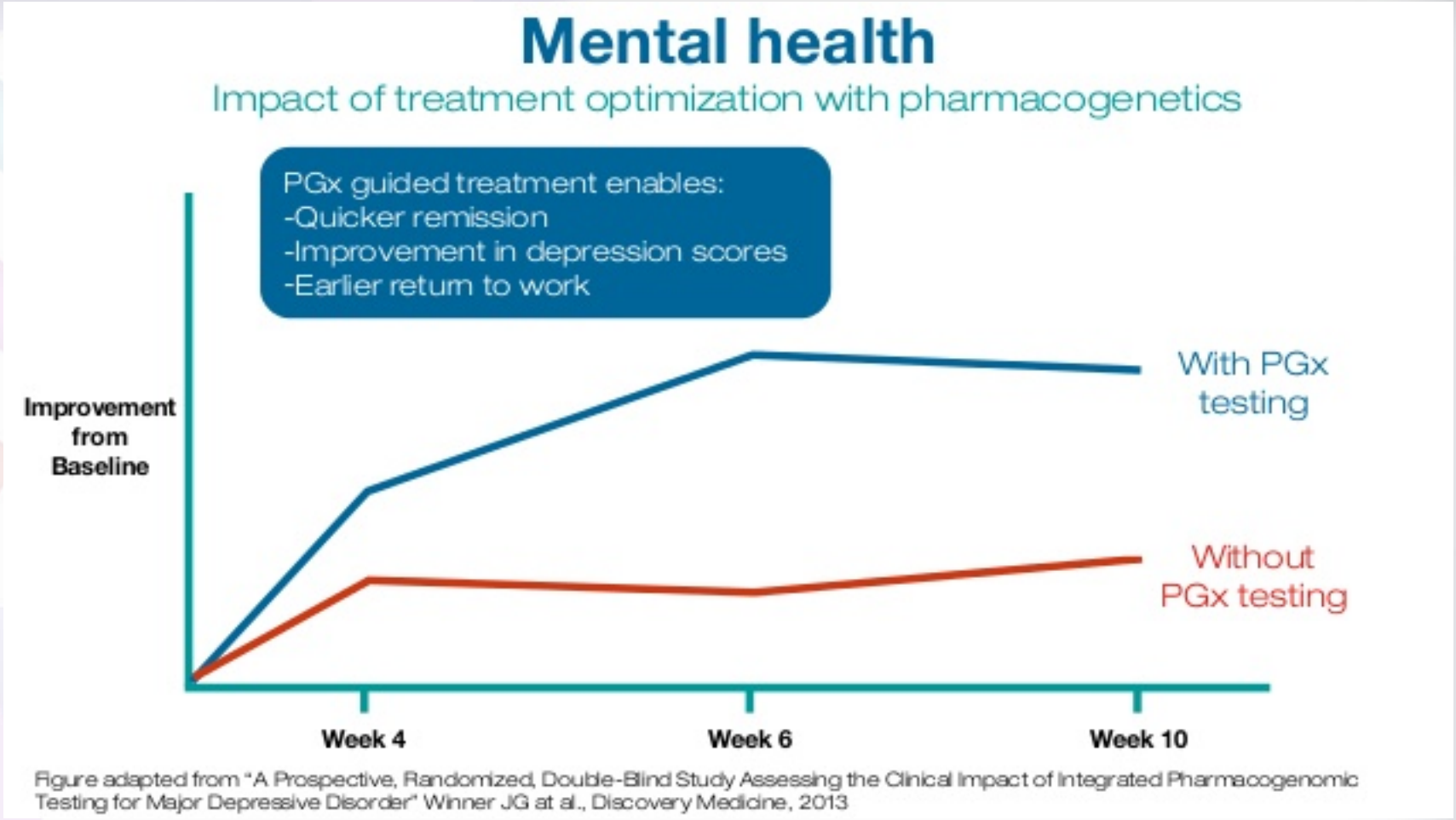


Figure adapted from "A Prospective, Randomized, Double-Blind Study Assessing the Clinical Impact of Integrated Pharmacogenomic Testing for Major Depressive Disorder" Winner JG at al., Discovery Medicine, 2013

- Figure 98: Mental Health (Medavie Blue Cross, 2017)

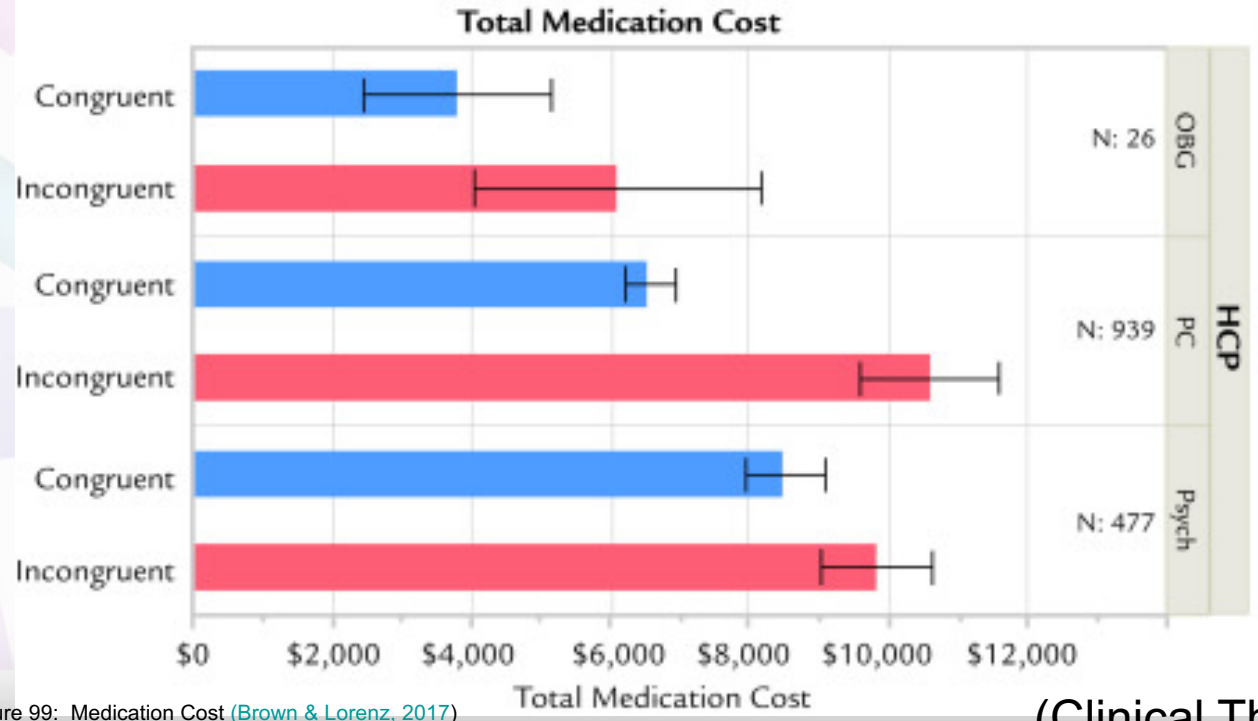
(Medavie Blue Cross, 2017)

Financials and Personalized Medicine

Medication Savings and Congruence According to Specialty

PCPs congruent with the combinatorial PGx testing recommendations saved payers and patients **$3998** compared with incongruent decisions ($P < .001$)

OB/GYNs who were congruent with the combinatorial PGx test results saved payers and patients **$2296** in medication costs over the course of the study ($P = 0.145$). **Psychiatrists** congruent with the combinatorial PGx test recommendations saved payers and patients **$1308** ($P = 0.013$).



Δ	*P*-value
$2,296	0.145
$3,988	<0.001
$1, 308	0.013

- Figure 99: Medication Cost (Brown & Lorenz, 2017)

(Clinical Therapeutics, 2017)

Other Benefits Personalized Medicine

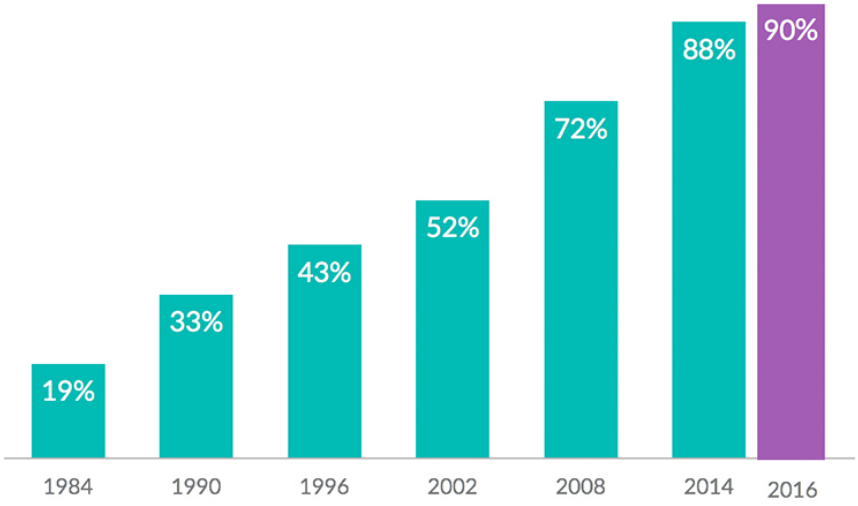
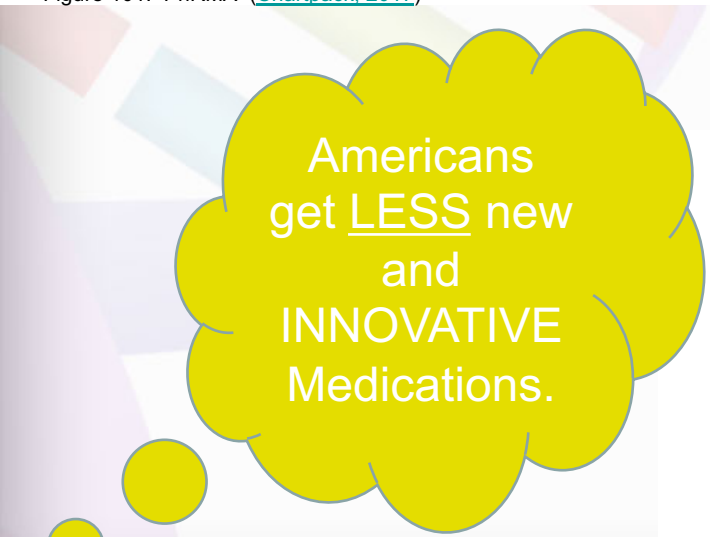
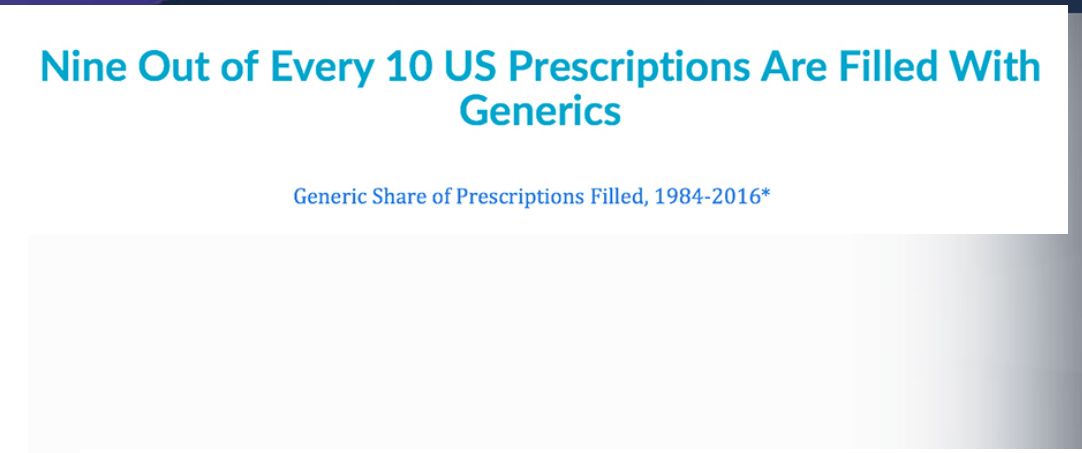
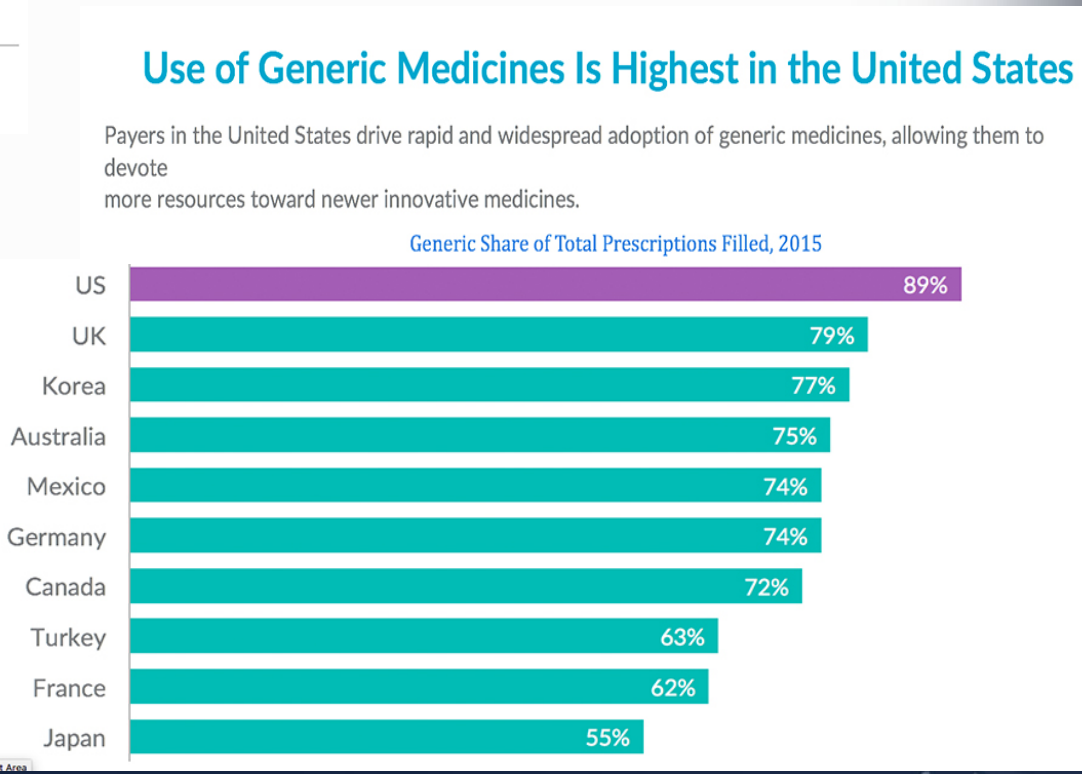


Figure 101: PhRMA (Chartpack, 2017)



- Figure 102: IMS Health (Chartpack, 2017)





Other Benefits Personalized Medicine

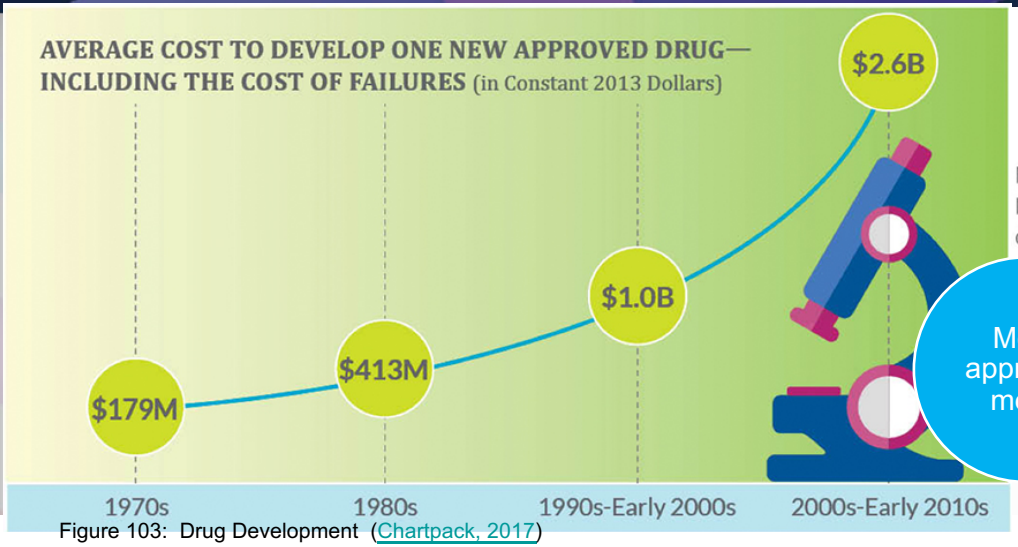
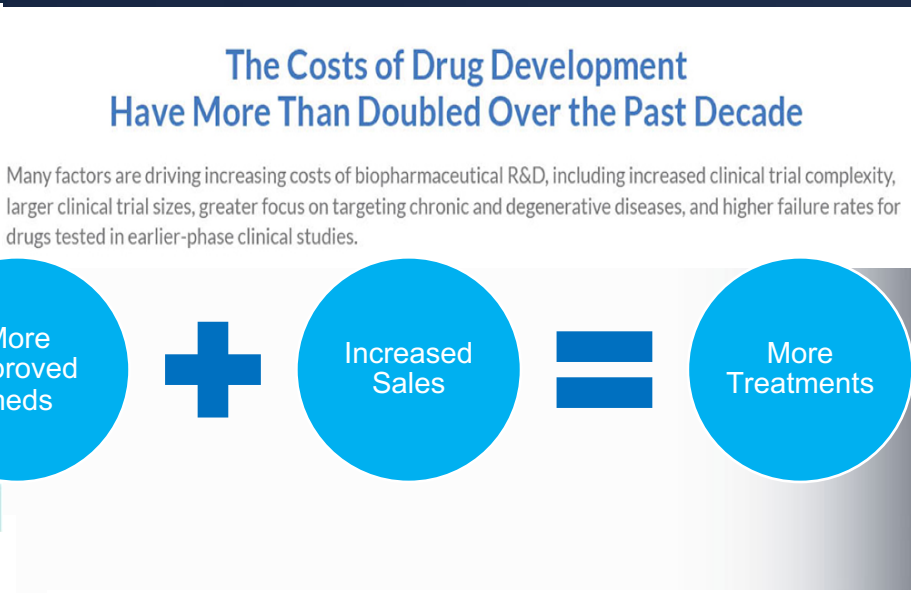


Figure 103: Drug Development (Chartpack, 2017)



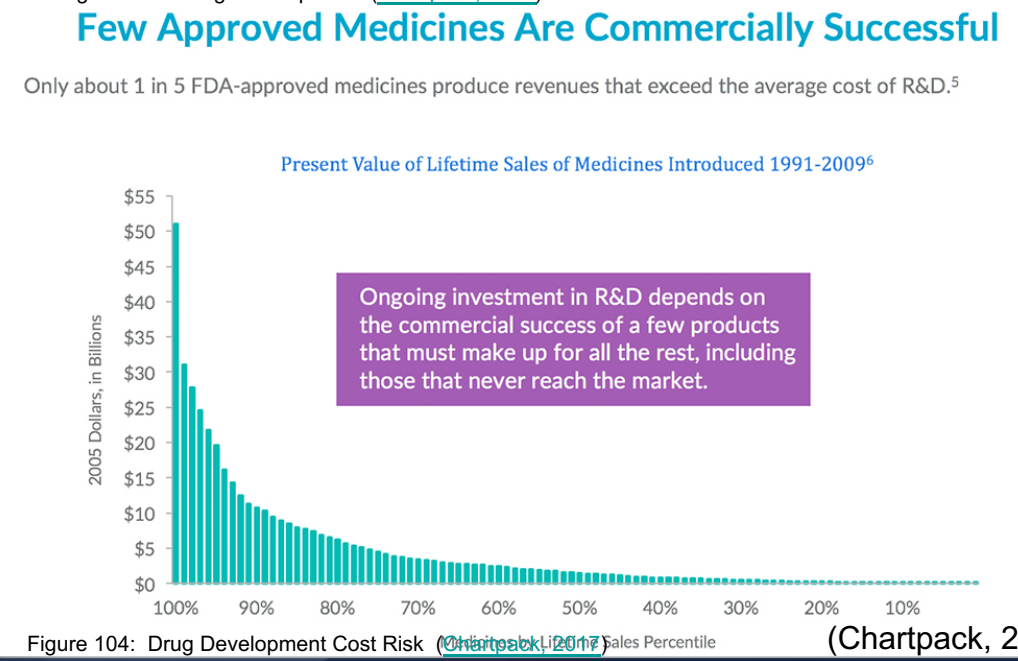


Figure 104: Drug Development Cost Risk (Chartpack, 2017)

(Chartpack, 2017)

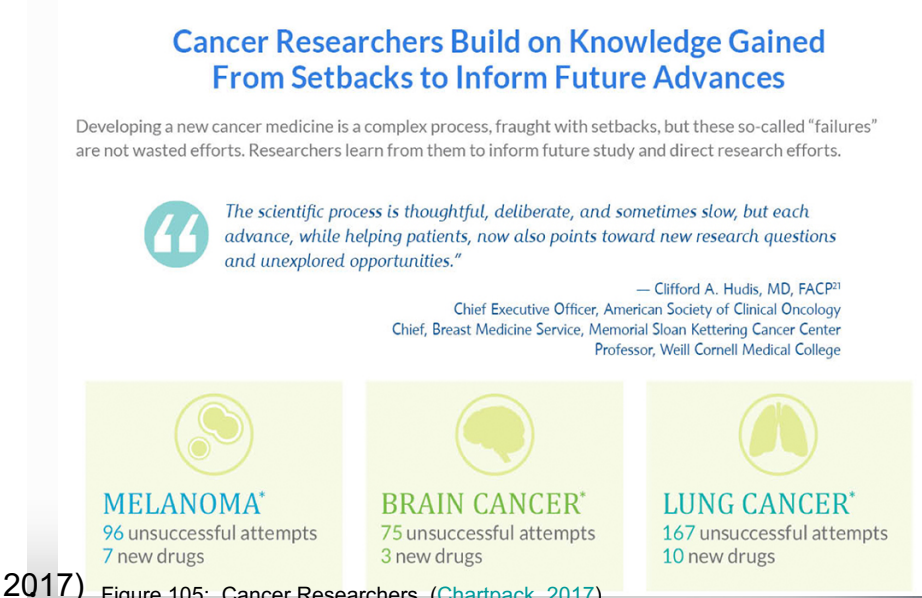


Figure 105: Cancer Researchers (Chartpack, 2017)

Other Benefits Personalized Medicine

New approaches for clinical trials:

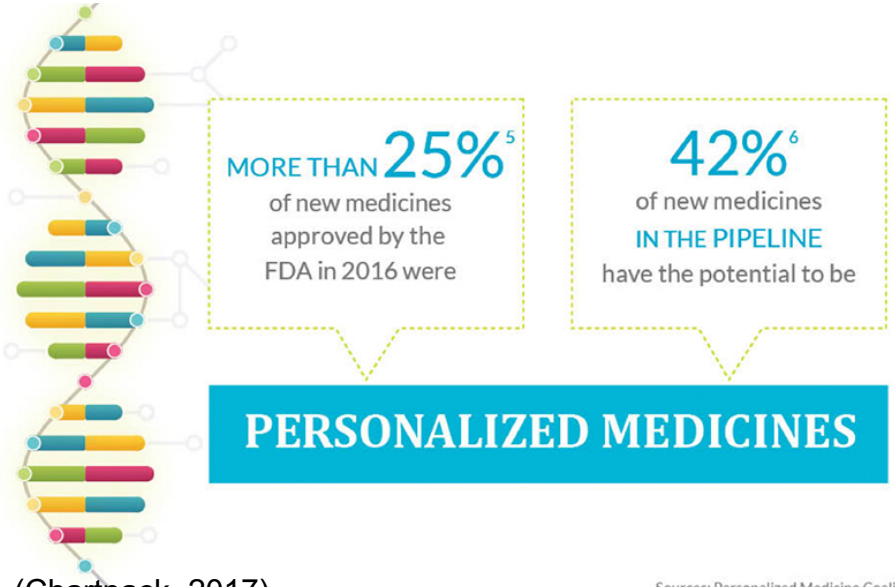
1. **Basket clinical trials:** Groups patients whose cancers contain the same genetic change (regardless of cancer type) and gives them all the same drug that targets this genetic change
2. **Umbrella clinical trials:** Groups patients with the same cancer type, but gives them differen drugs, matched to the genetic changes of eac of their tumours.

- Figure 107: New Approaches (Cancer.ca, 2017)

(Cancer.ca, 2017)

Biopharmaceutical Companies Are Committed to Advancing Personalized Medicine

In recent years, we have seen remarkable advances in targeted therapy, and the R&D pipeline has never been more promising.



(Chartpack, 2017)

- Figure 106: Biopharmaceutical Companies (Chartpack, 2017)

Sources: Personalized Medicine Coalition[5]; Tufts CS

Case Study: Jane

- Jane is a 38-year-old married, White female who has been treated for depression and anxiety since the age of 22. She has a personal history of abuse and is suffering flashbacks and nightmares. She has a medical history of migraine headaches, borderline obesity, and post-partum depression following the birth of her son 5 years ago. She has no known medication allergies. She has had no surgeries, seizures, head traumas, or concussions.
- Jane has also started drinking two glasses of wine per night on weeknights and “more on the weekends…I just feel better and I sleep, but I'm still tired.” She has not previously shared her tendency to abuse alcohol. She does not like the way she feels and wants to stop drinking.

(Leahy, 2017)

Case Study: Jane

- Jane's current symptoms include:
  - difficulty falling and staying asleep,
  - low motivation,
  - feeling fatigued,
  - depressed mood,
  - irritability,
  - headaches, occurring two to three times per week,
  - joint pain and muscle aches, and
  - decreased attention and concentration.
  - “I just know I have ADHD. I cannot focus at work and am not getting anything complete, I can’t seem to get it together”.

(Leahy, 2017)

Case Study: Jane

- **Jane's <u>past</u> psychotropic medications include:**
  - Fluoxetine (Prozac®) up to 80 mg daily—"It just stopped working after 4 years."
  - Venlafaxine (Effexor® XR) up to 300 mg daily—"My blood pressure started to increase."
  - Paroxetine (Paxil®) up to 40 mg daily—"I couldn't stand the 'brain zaps' when I missed a dose."
  - Alprazolam (Xanax®) 1 mg three times per day—"I would take more so my doctor cut me off."
  - Quetiapine (Seroquel®) 50 mg three times per day—"I gained weight because I would wake up and eat at night and became pre-diabetic."
- **Jane's <u>current</u> medications include:**
  - Sertraline (Zoloft®) 250 mg daily—"It helps a little, but I think it makes me more tired."
  - Aripiprazole (Abilify®) 5 mg daily—"I'm gaining weight and eating at night again, and I'm worried that I'll get diabetes."
  - Ortho Tri-Cyclen™ (oral contraceptive) daily—"I think it makes my headaches worse."
  - Tramadol (Ultram®) 50 mg up to four times per day as needed for headaches—"It doesn't really do much unless I take double the dose."

(Leahy, 2017)

Case Study: Jane

TABLE

GENETIC TESTING RESULTS, IMPLICATIONS, AND OPTIONS FROM CASE EXAMPLE

Gene	Results (Variant)	Implications	Potential Treatment Options
SLC6A4	S/S	Increased treatment resistance and adverse events	Non-SSRI antidepressant agents
5HT2C	C/C	Weight gain and metabolic syndrome with psychotropic agents	Caution with antipsychotic agents
CACNA1C	G/G	Normal genotype, no implications	Anticonvulsant mood stabilizers, lithium
ANK3	C/C	Normal genotype, no implications	Anticonvulsant, mood stabilizer, psychostimulant, and wake-promoting agents
ADRA2A	C/G	Decreased executive function	Psychostimulant or alpha-2 adrenergic agents
MC4R	C/A	Increased risk of adverse events and antipsychotic-induced weight gain	Non-antipsychotic mood stabilizing agents
BDNF	Val/Val	Normal genotype, no implications	Exercise to aide in maintaining working memory
GRIK3	C/C	Increased response to topiramate for alcohol abuse	Topiramate for alcohol abuse

- Figure 108: GeneticTesting1 (Leahy, 2017)

(Leahy, 2017)

Case Study Jane:

TABLE

GENETIC TESTING RESULTS, IMPLICATIONS, AND OPTIONS FROM CASE EXAMPLE

Gene	Results (Variant)	Implications	Potential Treatment Options
GRIK3	C/C	Increased response to topiramate for alcohol abuse	Topiramate for alcohol abuse
ORM1	A/G	Reduced response to opioid agonist medications	Monitor for opioid agent tolerance and dependence
COMT	Met/Met	Increased dopamine and executive function prefrontal cortex	Atypical antipsychotics
DRD2	C/Del	Increased risk for adverse events and decreased response to atypical antipsychotic agents	Non-antipsychotic mood stabilizing agents
MTHFR	C/C	Normal genotype, no implications	No specific treatments
CYP450	EM 2D6	No implications	None
	UM 2C19	Increased side effects, unpredictable treatment response	May need increased or more frequent dosing
	EM 3A4/5	No implications	None
	UM 2B6	Increased side effects, unpredictable treatment response	May need increased or more frequent dosing
	PM 2C9	Increased failure and side effects due to increased exposure to drug metabolites	May need decreased or less frequent dosing
	EM 1A2	No implications	None

- Figure 109: GeneticTesting2 (Leahy, 2017)

(Leahy, 2017)

Case Study Jane:

- The psychiatric advanced practice nurse meets with Jane to review and develop a personalized medication plan. Over the years, Jane has been prescribed three different selective serotonin reuptake inhibitor (SSRI) antidepressant agents.
- Her testing reveals the S/S variant of the SLC6A4 gene, which indicates the potential for treatment resistance and adverse events. In addition she is had higher risk for elevated cortisol release under stress placing her at risk for PTSD and anxiety.
- In addition, Jane's genetic profile reveals ultrarapid metabolism of drugs metabolized by CYP450 2C19.

(Leahy, 2017)

Case Study Jane:

- So are Jane's Medications appropriate?

Case Study Jane:

Answer: NO

- Jane's failure with SSRIs and high doses of fluoxetine and sertraline (both metabolized by the 2C19 enzyme) and her lack of response to tramadol (metabolized by the 2B6 enzyme) at lower doses make sense.
- Thus, treating her depressive symptoms and headaches going forward will require an alternate approach.

Case Study Jane:

- Similarly, Jane has the C/G variant for the ADRA2A gene, which also contributes to decreased ability to focus.
- These results explain Jane's complaints of decreased attention and concentration as well as her experiences of taking more than the prescribed doses of alprazolam and tramadol and her increasing consumption of alcohol.
- She exclaims excitedly “I knew I had ADHD” Looking at the reports she gets super excited that it recommends psychostimulants for treatment.

(Leahy, 2017)

Case Study Jane:

- Would a stimulant be appropriate for Jane?

Answer: NO

- Jane's profile also reveals the Met/Met variant on the COMT gene.
- This genotype implies that Jane has increased dopamine and executive function in the prefrontal cortex.
- Based on this gene she would respond better to atypical antipsychotics.

Case Study Jane:

- Jane **reports gaining weight** when prescribed the atypical antipsychotic medications as add-ons for treatment-resistant depression.
- Her genetic testing reveals the C/C variant for the 5HT2C gene, the C/A variant for the MC4R gene.
- These variants suggest difficulty with feeding and satiety and can be worse with the application of atypical antipsychotics.
- In addition she has the C/Del variant for the DRD2 gene.

(Leahy, 2017)

Case Study Jane:

- So, would an atypical antipsychotic be appropriate for Jane?

Answer: NO

- Her DRD2 deletion puts her at increased risk of less response to atypical antipsychotics in addition to side effects like EPS.
- All of these variants indicate that Jane may experience adverse events, including weight gain, related to the antipsychotic medications and that alternative mood stabilizing agents should be considered.
- Jane's profile also indicates the potential for decreased response to SSRIs and weight gain related to antipsychotic agents: **tapering and discontinuing the sertraline and aripiprazole would be indicated.**

Case Study Jane:

- Jane's genotype reveals a C/C variant for GRIK1 which places her at higher risk for excessive glutamate firing, met/met variant for COMT excessive dopamine in the prefrontal cortex, and an A/G variant for OPRM1 increased risk of non response to opiods putting her at high risk for alcohol and opioid depenedence, all of which offer insights into potential risks and treatments related to substance use.
- As Jane has required greater doses of tramadol to relieve her headaches, increased doses of alprazolam, and has also been increasing her alcohol consumption.
- In addition, because Jane has "needed" to take double the dose of **tramadol** for relief from her headaches, it **should also be tapered and discontinued**.
- As Jane remains depressed with low motivation, fatigue, decreased attention and concentration, as well as chronic headaches and increased alcohol use to the point of being diagnosed with Alcohol Use Disorder, a new pharmacotherapy regimen is required.
- She has also indicated a history of trauma yielding a suspected diagnosis of PTSD. She also meets criteria for ADHD.

(Leahy, 2017)

Case Study Jane:

- What would be a good choice to trial for Jane?
  - What medication would help treat her mood swing, chronic migraines, alcohol use, and PTSD?

Case Study Jane:

- Consideration may also be given to a trial of topiramate, as Jane's C/C variant for GRIK1 indicates that she, being of European descent, should respond to this agent for abstinence from alcohol abuse.
- Topiramate is also a U.S. Food and Drug Administration–approved medication for migraine headache prophylaxis and an off-label treatment for sleep-related eating, which is causing her weight gain, and nightmares related to PTSD.
- Jane may experience multiple benefits from this single agent.
- However, caution is advised, as topiramate is a CYP3A4 substrate, which may increase the potential for adverse events when taken with the oral contraceptive.
- In fact, topiramate may make her birth control less effective, so education may need to be done about alternative birth control measures.

(Leahy, 2017)

Case Study Jane:

- Lastly, if Jane's headaches persist, a non-opioid and non-controlled medication would be consistent with her genotypes on OPRM1 and COMT.
- Consideration may be given to naproxen, a nonsteroidal anti-inflammatory analgesic metabolized by CYP2C9.
- As Jane is a poor metabolizer for CYP2C9, lower doses or less frequent dosing of naproxen would be indicated.
- She may also benefit from naltrexone as some patients with OPRM1 respond better to their own endogenous opioids.

(Leahy, 2017)

Case Study Jane:

- What may be some other considerations for Jane?

Case Study Jane:

- Consideration might be given to a trial of Guanfacine, a non-SSRI ADHD agent, which will not directly enhance dopamine in the prefrontal cortex. This choice would be consistent with Jane's COMT, OPRM1, ADRA2A genotypes, as it would enhance executive functioning without the risk of abuse.
- Jane may also benefit from treatments like TMS to effectively treat mood and her symptoms of inattention and focus.
- Gabapentin or long acting preparations of gabapentin may be considered to help with alcohol dependence, anxiety, and chronic pain in addition to migraine headaches.

(Leahy, 2017)

Case Study Jane:

- If continued difficulty with mood symptoms persisted, it may be warranted to trial newer partial agonist atypical antipsychotics like cariparazine which works on DRD3 before DRD2 or brexpiprazole since it works on alpha adrenergic receptors and doesn't completely block dopamine making it a bit more tolerable to her genetic profile if needed.
- An antidepressant like vortioxetine, vilazadone may also be indicated since they work both pre and post synaptically.
- SNRIs may have been considered if she hadn't had withdrawal affects with Paxil.

(Leahy, 2017)

Questions

- ????

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