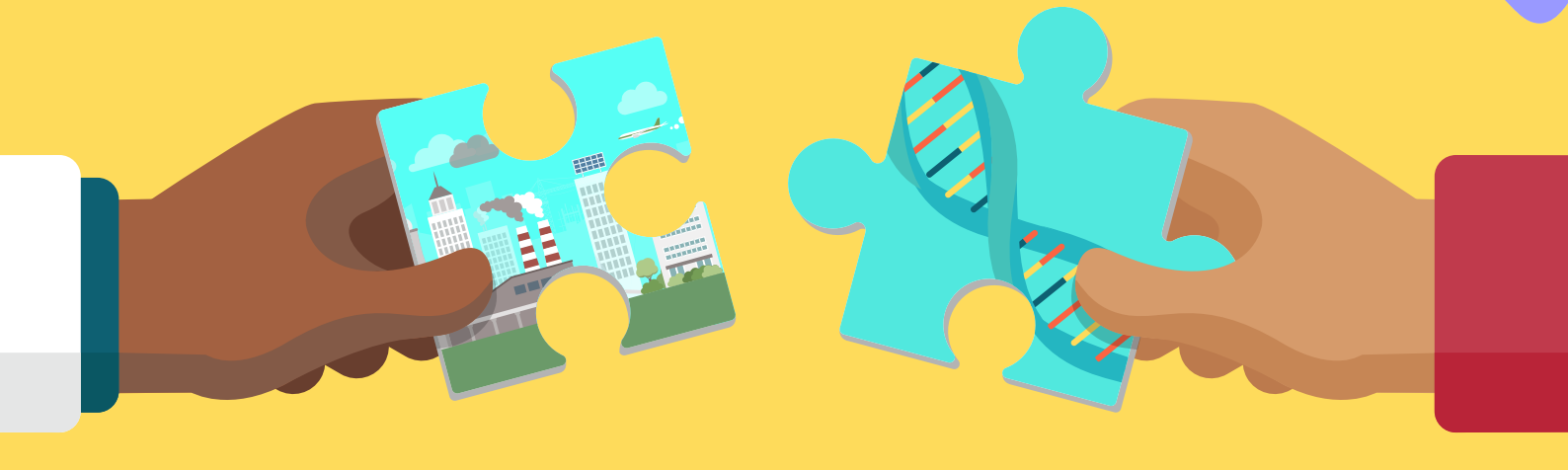
TECHNOLOGY NETWORKS

Over recent years, the medical field has placed increasing focus on making personalized medicine, whereby our medical treatment plans are tailored to us as individuals, more mainstream across the globe.

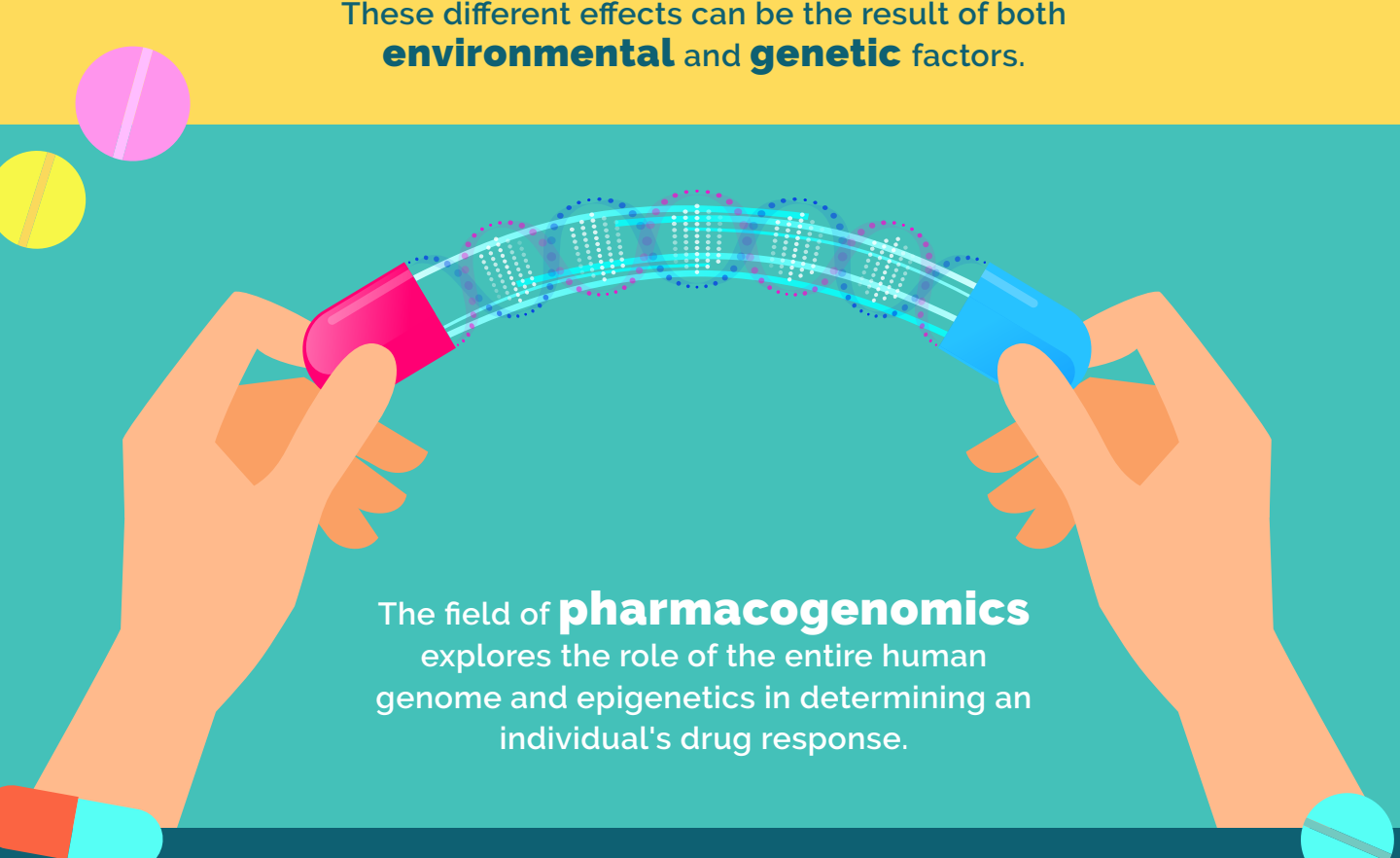
A key area of personalized medicine is **pharmacology**.

Many marketed drugs are prescribed by medical professionals as a "one size fits all" medication.

However, these medications can actually elicit **different** effects in **different** people.



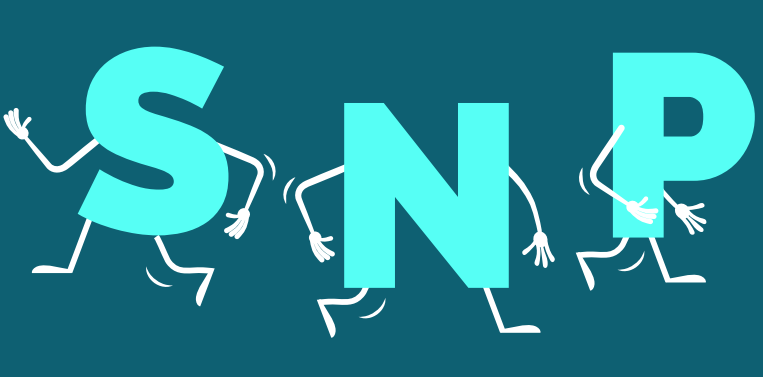
These different effects can be the result of both **environmental** and **genetic** factors.



The field of **pharmacogenomics** explores the role of the entire human genome and epigenetics in determining an individual's drug response.

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variations that exist.

Each SNP represents a difference in a nucleotide; for example, an SNP may replace the nucleotide cytosine with the nucleotide thymine.



If an SNP occurs in the coding region of the genome then there can be significant structural and functional alterations to the protein that is subsequently produced.

How does this link to drug response? Well, pharmacogenomics considers whether the altered variant form of the protein is involved in either:

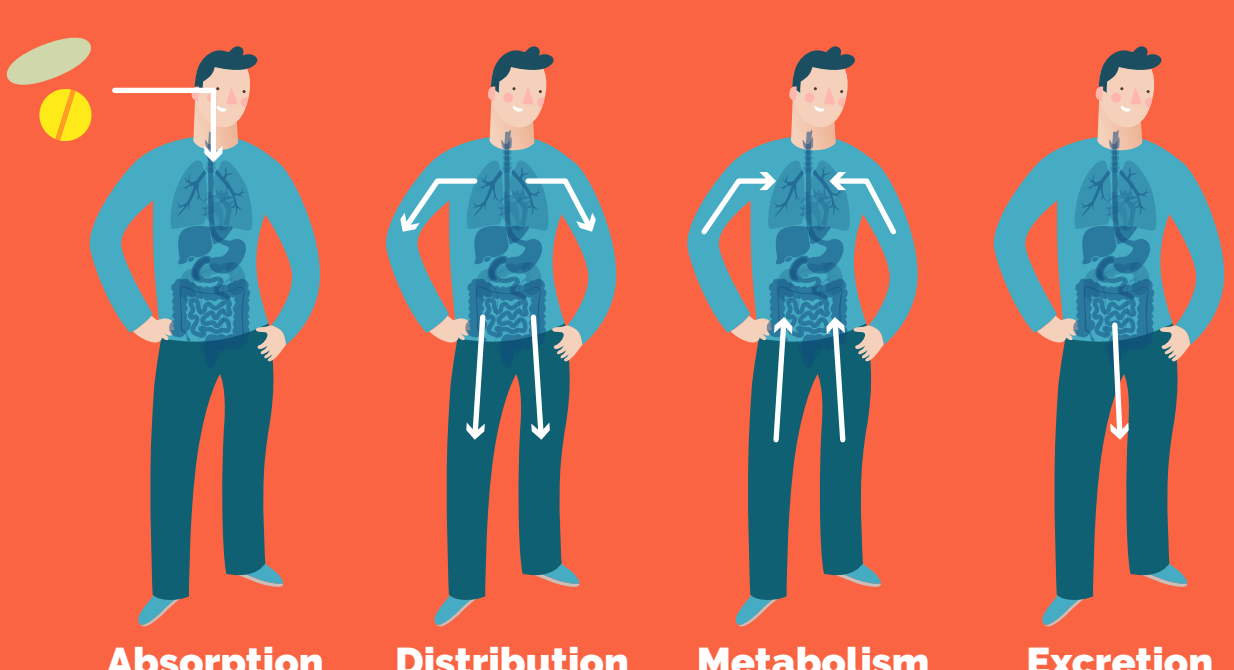
Pharmacokinetics

OR

Pharmacodynamics

of a therapeutic compound

Every therapeutic that enters the body follows an identical process of absorption, distribution, metabolism and excretion (ADME) – but one that is specific to that drug.



Pharmacokinetics refers to the **sum** of these processes.

Let's look at how genetic polymorphisms can impact different stages of this process...

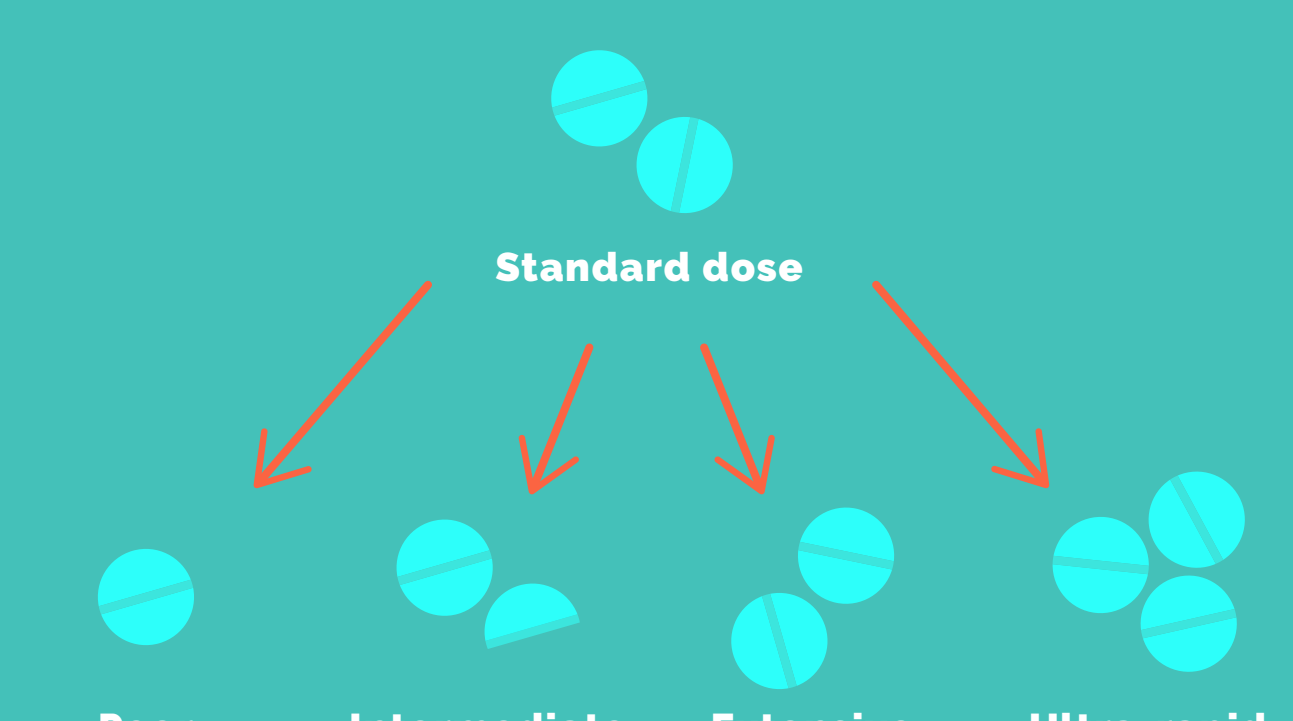
Pharmacokinetics – drug metabolizing enzymes

The cytochrome P450 (CYP) superfamily of Phase I enzymes are arguably the most important enzymes in drug metabolism. They are involved in drug deactivation and bioactivation.[1,2]

The CYP genes encoding the superfamily of enzymes are **very** polymorphic.

Depending on which polymorphism an individual possesses they are classified into one of four phenotypes:

Based on these phenotypes we can assume that dosage needs to be personalized, for example:[1]



The most pharmacologically and clinically relevant CYP polymorphisms are:

CYP2D6, CYP2C9 and CYP2C19[3]

Let's look at **CYP2D6** as an example.

CYP2D6 is **highly** polymorphic, and is implicated in the metabolism of up to 25% of drugs routinely used in healthcare settings, such as:

Name:
Date:

ANTIDEPRESSANTS
e.g. amitriptyline, citalopram, clomipramine

ANTIPSYCHOTICS
e.g. chlorpromazine, clozapine, haloperidol

ANTIARRHYTHMICS
e.g. flecainide, mexiletine, propafenone

BETA-BLOCKERS
e.g. carveditol, metoprolol, yohimbine, timolol

OPIOID ANALGESICS
e.g. codeine, dihydrocodeine, morphine

ANTICANCER AGENTS
e.g. debrisoquine, gefitnib, sparteine

Signature:

CYP2D6 and codeine:

Codeine is a pro-drug and is metabolized to morphine by CYP2D6:

Codeine (pro-drug) → CYP2D6 → **Morphine** (active)

STANDARD DOSE OF CODEINE

CYP2D6 ACTIVITY	LEVEL OF ACTIVE DRUG	TYPE OF METABOLIZER
	Morphine *lower than normal*	Poor metabolizer
	Morphine *normal*	Extensive & intermediate metabolizer
	Morphine *higher than normal*	Ultra-rapid metabolizer

The FDA drug label for codeine states that even at labeled dosage regimens, ultra-rapid metabolizers may experience life-threatening or fatal respiratory depression or other signs of overdose.

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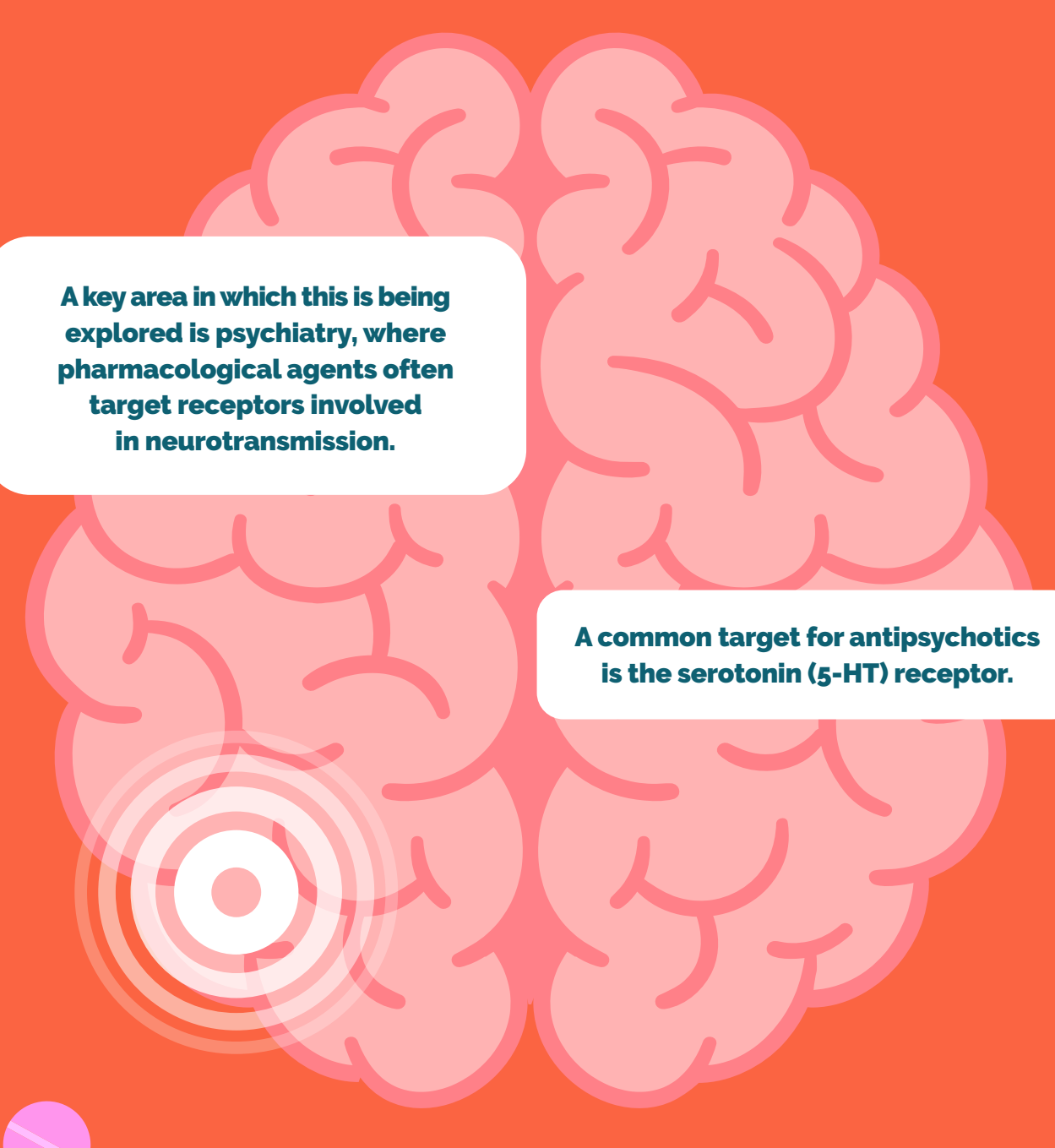
Pharmacodynamics – drug targets

Drug targets are often proteins. Genetic polymorphisms can therefore alter the encoded protein to which the drug would typically bind and impact the drug's mode of action and efficacy.



The 5-HT transporter (5-HTT) gene (SCLC6A4) has a common length polymorphism that causes a partial deletion of a tandem repeat sequence within its promoter region, resulting in lower expression of the transporter.

Studies have shown varying responses in patients either heterozygous or homozygous for the allele to drugs such as fluvoxamine and nortriptyline in major depression.[4,5]

Potential benefits of pharmacogenomics

Challenges in pharmacogenomics

- Quantifying the economic impact and cost-effectiveness of pharmacogenomic profiling
- Implementing next generation sequencing as a routine clinical measurement
- Distinguishing between functional driver mutations and non-functional mutations when selecting targeted therapies for pharmacological intervention

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4. Smeraldi et al. (1998). Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Molecular Psychiatry*. DOI: 10.1038/sj.mp.4000425.

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