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Importance of *TPMT* and *NUDT15* Genotype Testing to guide dosing of 6-mercaptopurine in adult patients with acute lymphoblastic leukemia (ALL)

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April + June 2023

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Learning Objectives

- Understand what acute lymphoblastic leukemia (ALL) is and the underlying patho-physiology of the disease
- Describe role of 6-mercaptopurine in treatment and understand its mechanism of action
- Understand the role of TPMT and NUDT15 in the metabolism and detoxification of 6-mercaptopurine
- Identify the common variant alleles that contribute to reduced or absent TPMT and/or NUDT15 enzymatic activity and link this to increased risk of myelosuppression
- Understand the importance of genetic testing in patients receiving 6-mercaptopurine and be able to implement dose modifications according to a patient's phenotype

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Acute lymphoblastic leukemia (ALL)

Introduction

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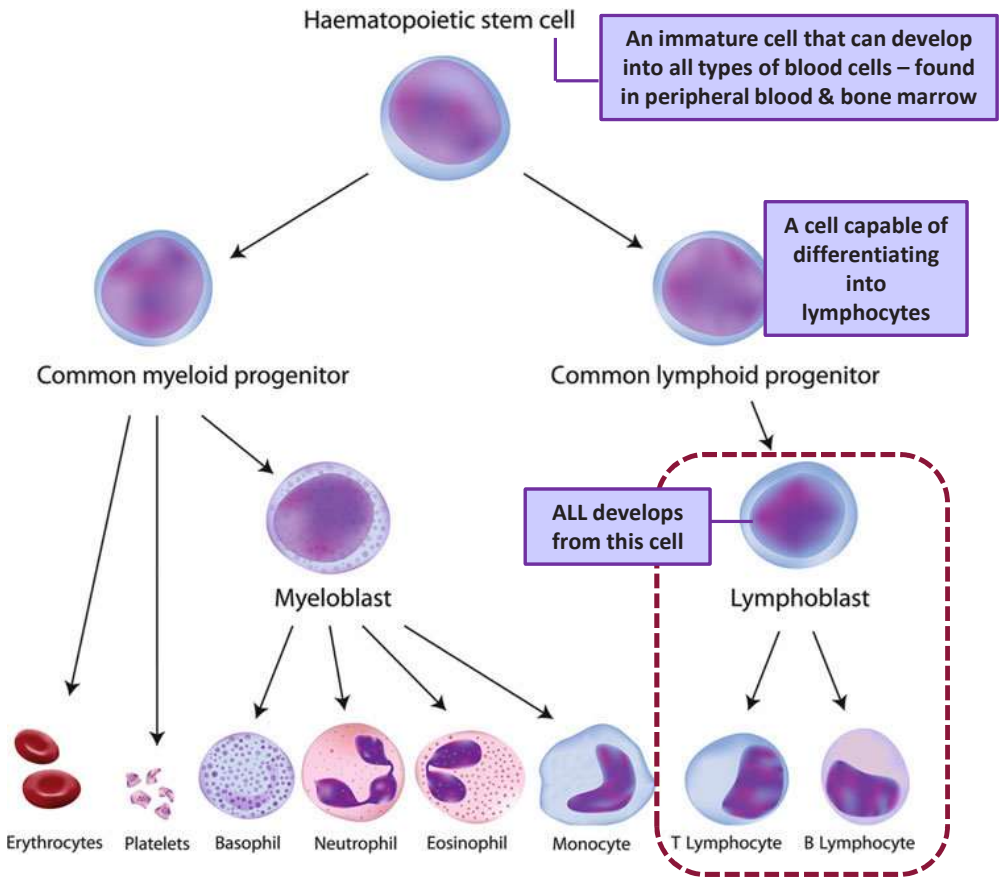
What is Acute lymphoblastic leukemia (ALL)

- ALL is a relatively rare malignancy that affects around 790 people each year in the UK[1]
- It is a lymphoid leukemia which results from the overproduction of immature lymphocytes (lymphoblasts)
- Broadly categorised into B-ALL or T-ALL based on their lineage



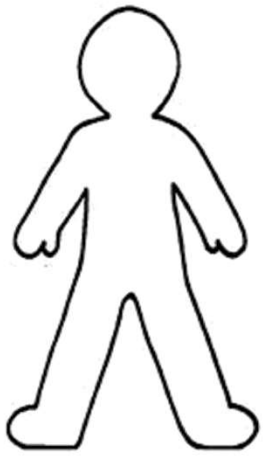
Adapted from https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [1]

Statistics

*declines with age

Adapted from https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about [1]

Cases

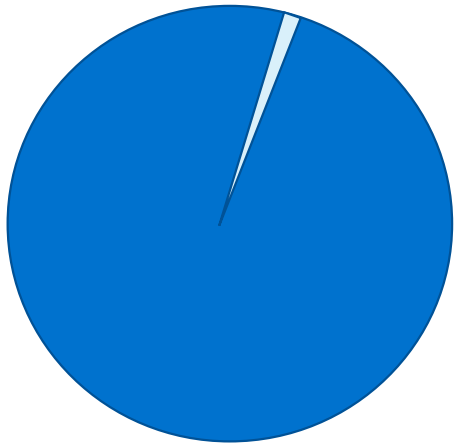


791

Age

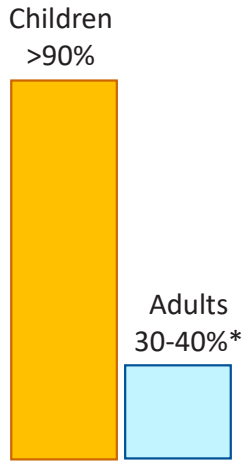
Highest incidence in children aged 0-4years

Proportion



<1% of total UK cancer cases

Survival

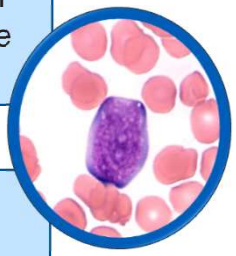


>90% for children

- ALL incidence is strongly related to age and has a bimodal age incidence; constitutes majority of leukemias in childhood but <5% of adult leukemias[1]
- Note: scope of this presentation will cover testing and dosing in adults >25y only

Pathophysiology

Malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived progenitor cell due to a series of acquired genetic aberrations



Overproduction of immature lymphocytes (lymphoblasts) and high circulating number of blasts

Bone Marrow

Systemic Circulation

Replacement of marrow by malignant cells
Accumulation of lymphoblasts will prevent bone marrow production of cells such as red blood cells, neutrophils and platelets

Infection, bleeding, anaemia, thrombocytopenia (low platelets), neutropenia (low neutrophils)

Leukemic infiltration
Lymphoblasts enter the systemic circulation and can collect in certain areas of the body e.g. the central nervous system (CNS), testes and lymph nodes (LN)

Organ infiltration (hepatomegaly, splenomegaly)

LN enlargement

CNS symptoms
headaches, blurred vision, impaired balance, nausea

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Acute lymphoblastic leukemia (ALL)

Treatment

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Treatment

- In general, treatment of ALL consists of four phases[1]:

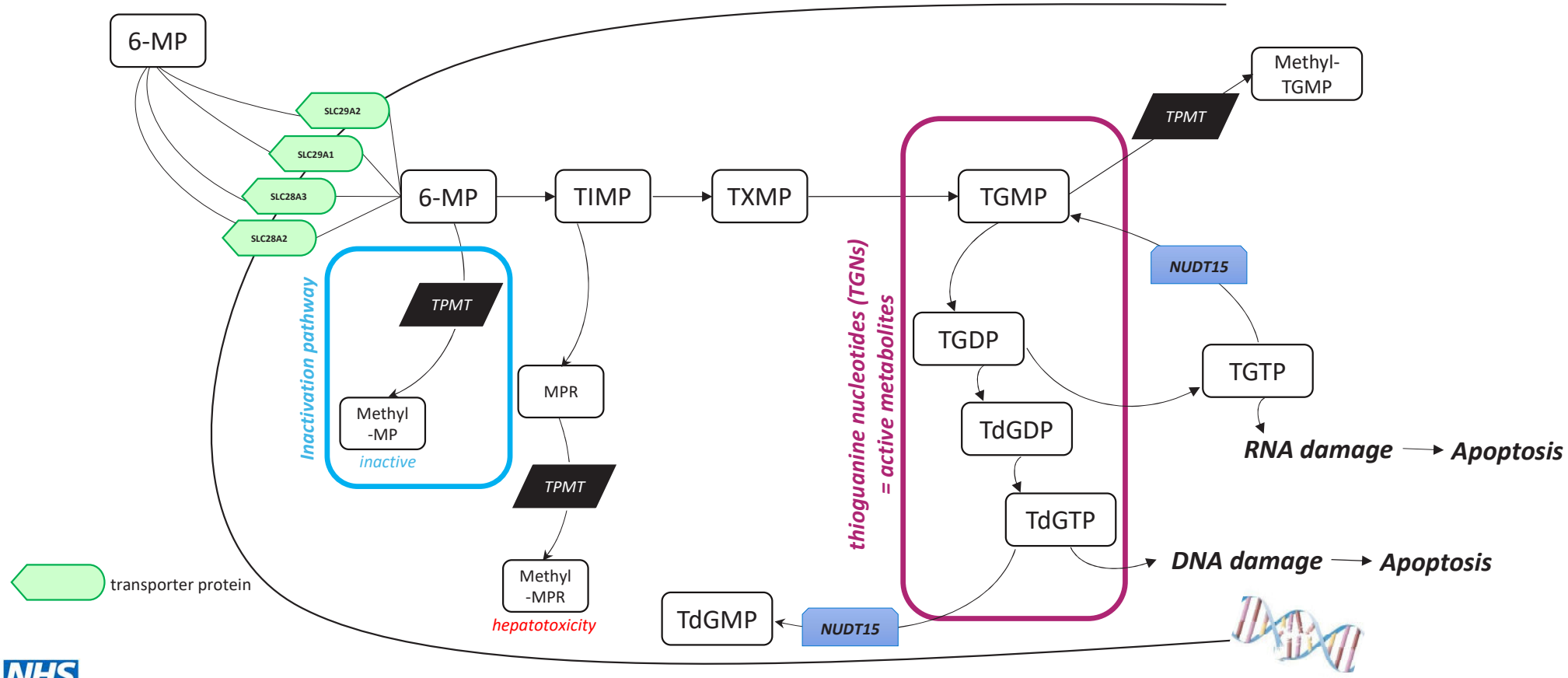
CNS Prophylaxis: starts during induction and continues throughout all phases of treatment – ***lymphoblasts often infiltrate the spinal fluid and meninges***

- Likely duration of therapy is 2.5-3 years

What is 6-mercaptopurine (6-MP)?

- 6-MP is a thiopurine that is used in the induction, consolidation and maintenance phases of adult ALL treatment protocols
- It is an oral prodrug that is metabolised to active thioguanine nucleotides (TGNs); these are incorporated into DNA in competition with natural guanine
- Incorporation of TGNs into DNA results in random methylation, base pair mismatching, double strand breaks and ultimately cell apoptosis
- Thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) are key enzymes in the metabolism and inactivation of 6-MP[2]

Metabolism of 6MP



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Thiopurine S-methyl transferase

TPMT

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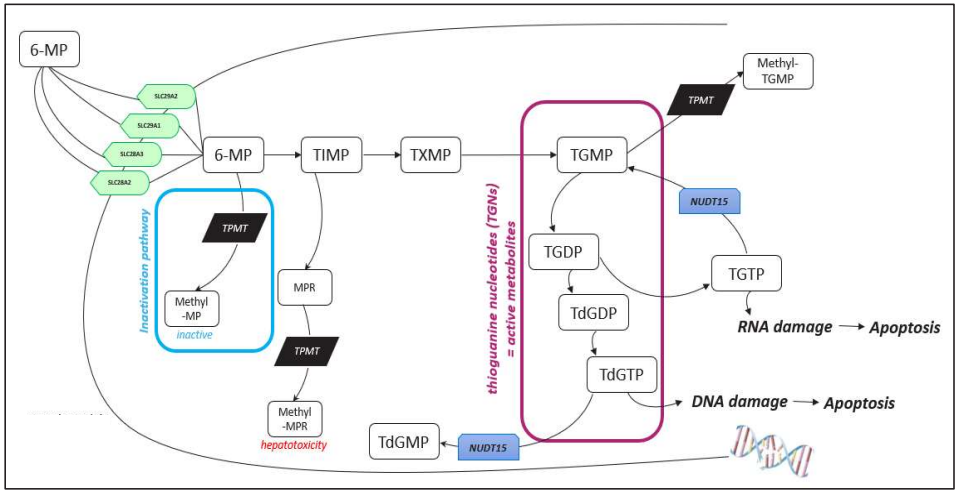
Thiopurine S-methyl transferase (TPMT)

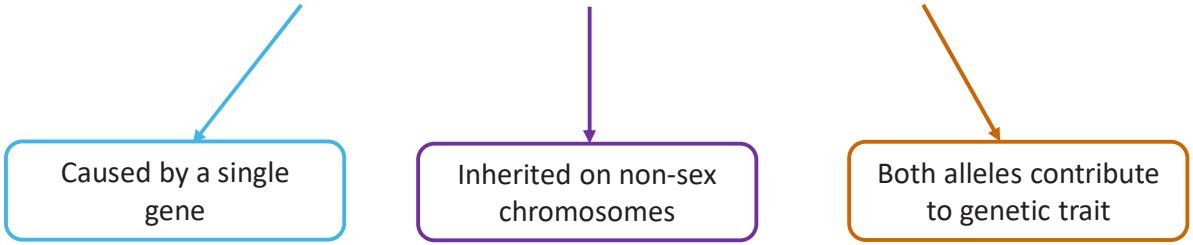
- TPMT is a cytosolic enzyme that has a key role in the metabolism of 6-MP[2]
- It catalyses the S-methylation of 6-MP to an inactive methyl-mercaptopurine base leaving less parent drug available for anabolism to active TGNs[2]



- In order to exert its cytotoxic effects, 6-MP requires metabolism to TGNs by a multistep process
- TPMT prevents TGN production by methylating 6-MP
- *Reduced activity of TPMT = less inactivation of 6-MP = increased effect and more toxicity to include severe bone marrow suppression*

TPMT Genotype

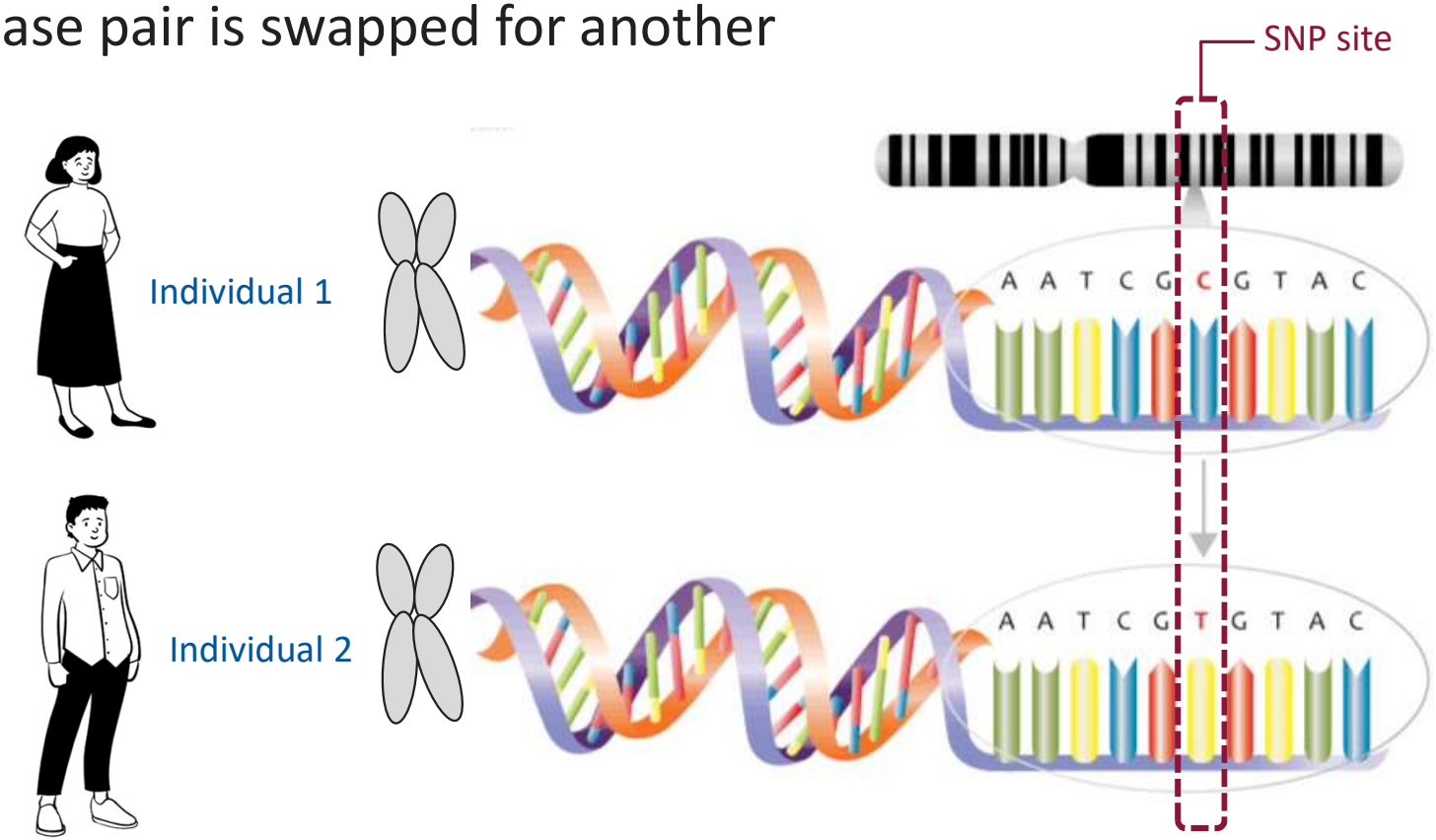
- TPMT encoded by the *TPMT* gene that is located on chromosome 6p 22.3[3]
- TPMT activity is inherited as a **monogenic** **autosomal** **codominant** trait[2]



- Multiple single nucleotide polymorphisms (SNPs) have been identified in the *TPMT* gene which determine the level of TPMT enzymatic activity (phenotype)
- There are three well characterised SNPs which result in the production of unstable proteins subject to increased proteolytic degradation and resultant loss of TPMT enzymatic activity[2]

Single Nucleotide Polymorphisms (SNPs)

- SNPs are a form of genetic variation between individuals where a single DNA base pair is swapped for another



Adapted from diagram by Genomics Education Programme, HEE[4]

TPMT SNPs

- 1 in 300 individuals inherit TPMT deficiency as an autosomal trait[5]
- The three SNPs listed below account for >95% of low activity phenotypes and produce the most common no function alleles[2]
- Adult patients with a confirmed diagnosis of ALL and proposed treatment with 6-MP should be genotyped for the following variants[2,3]

GENETIC VARIANT		EFFECT	
Star (*) Allele	**HGVS cDNA Nomenclature**	**Amino acid substitution**	**Ethnicity Prevalence** (frequency of SNPs variable across ethnicities)
*Note: TPMT*1 = the normal function allele and confers normal enzyme activity (wildtype)*			
TPMT*2	c.238 G>C	Ala80Pro	Most common in African patients (0.5%) Also found in Latino (0.35%) & European (0.2%) patients. Rare in Asian populations.
TPMT*3A (most common)	c.460 G>A c.719 A>G	Ala154Thr Tyr240Cys *2 nucleotide transition mutations*	Most common in Latino (4.2%) & European (3.4%) patients. <0.5% in Central/South and East Asian populations.
TMPT*3B	c.460 G>A	Ala154Thr	Most common in European (0.3%) and Latino (0.2%) patients. Rare in East-Asian and African patients
TPMT*3C	c.719 A>G	Tyr240Cys	Predominant variant in black patients (12.2%). Found commonly in African (2.4%) and East-Asian (1.6%) patients.

HGVS: Human Genome Variation Society, Ala: alanine, Pro: proline, Thr: threonine, Tyr: tyrosine, Cys: cysteine

Linking TPMT Genotype and Phenotype

- Individuals will have two alleles for the *TPMT* gene
- Since TPMT enzyme expression is a codominant trait, it is the combination of alleles an individual has (diplotype) that will determine their phenotype
- An individual may be homozygous (two identical alleles) or heterozygous (two different alleles) for the trait
- Functional variants in the *TPMT* gene produce a trimodal distribution of enzyme activity (normal, intermediate and poor)[3]

Normal Metaboliser

- An individual with 2 normal function alleles

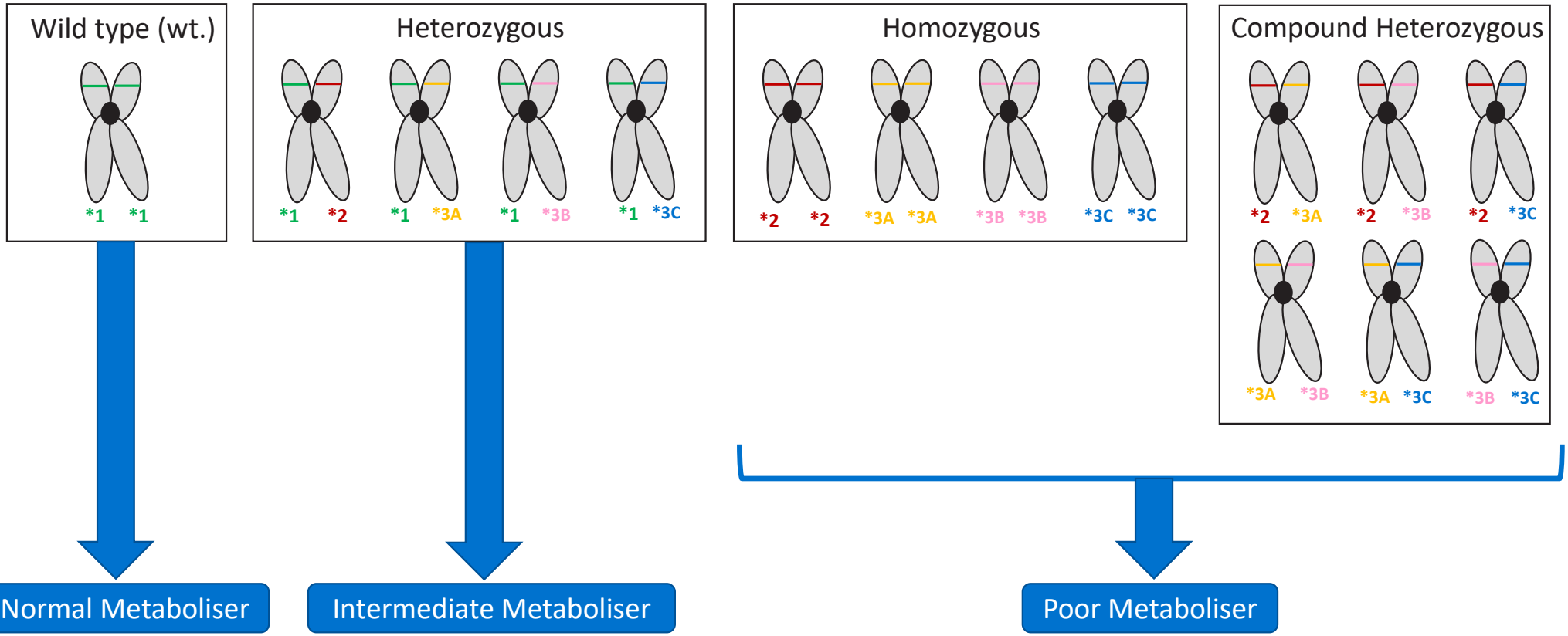
Intermediate Metaboliser

- An individual with one normal function allele PLUS one no function allele

Poor Metaboliser

- An individual with two no function alleles

Linking TPMT Genotype and Phenotype



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Nudix hydrolase 15

NUDT15

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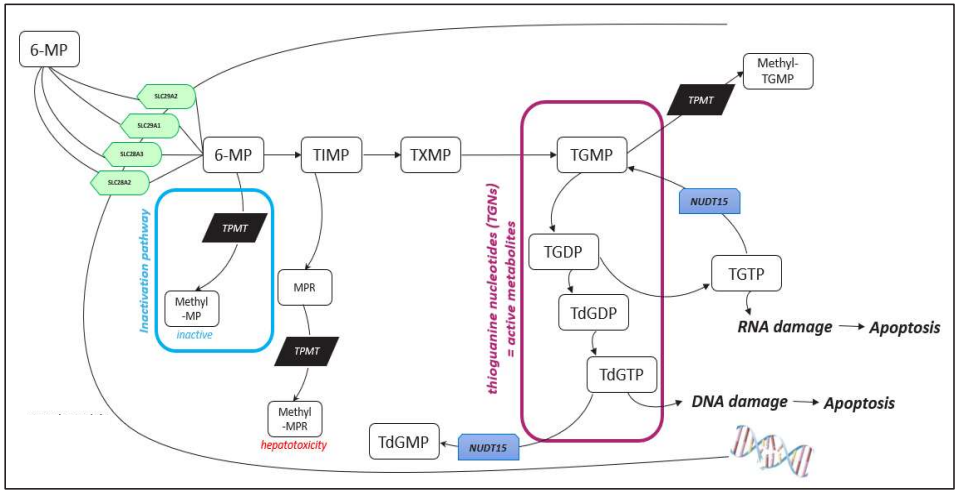
Nudix hydrolase 15 (NUDT15)

- *NUDT15* located on chromosome 13 encodes the Nudix hydrolase 15 protein[3]
- NUDT15 = a nucleotide diphosphatase that hydrolyses active and cytotoxic thiodeoxyguanine triphosphate (TdGTP) to its less toxic monophosphate form (TdGMP)[3]



- NUDT15 reduces amount of TGNs for incorporation into DNA, reduces the DNA toxic effects of 6-MP
- *Reduced NUDT15 activity = less NUDT15-mediated degradation of TdGTP= more TdGTP available for incorporation into DNA = increased DNA damage and cell death*

NUDT15 Variants

- Like *TPMT*, the *NUDT15* gene is polymorphic; there are 21 known variant alleles[3]
- *NUDT15* variants are less well described than those of *TPMT* and most are extremely rare
- Deficiency of NUDT15 is found in <1% of individuals with European or African ancestry[3]
- More common (~2%) in individuals with East Asian ancestry (e.g. Korea, China, Japan)[2]

GENETIC VARIANT		EFFECT	
Star (*) Allele	**HGVS cDNA Nomenclature**	**Amino acid substitution**	**Ethnicity Prevalence** (frequency of SNPs variable across ethnicities)
*Note: NUDT15*1 = the normal function allele and normal enzyme activity (wildtype)*			
NUDT15*3	C415 C>T	Arg139Cys	Found most commonly in Central/South (6.7%) and East-Asian (6.1%) populations >1% in Latine and European populations

HGVS: Human Genome Variation Society, Arg: arginine, Cys: cysteine

Linking NUDT15 Genotype and Phenotype

- Individuals will have two alleles for the *NUDT15* gene
- An individual may be homozygous (two identical alleles) or heterozygous (two different alleles) for the trait
- The amino acid change Arg139Cys results in an unstable protein which almost no enzymatic activity[3]

Normal Metaboliser

- An individual with 2 normal function alleles

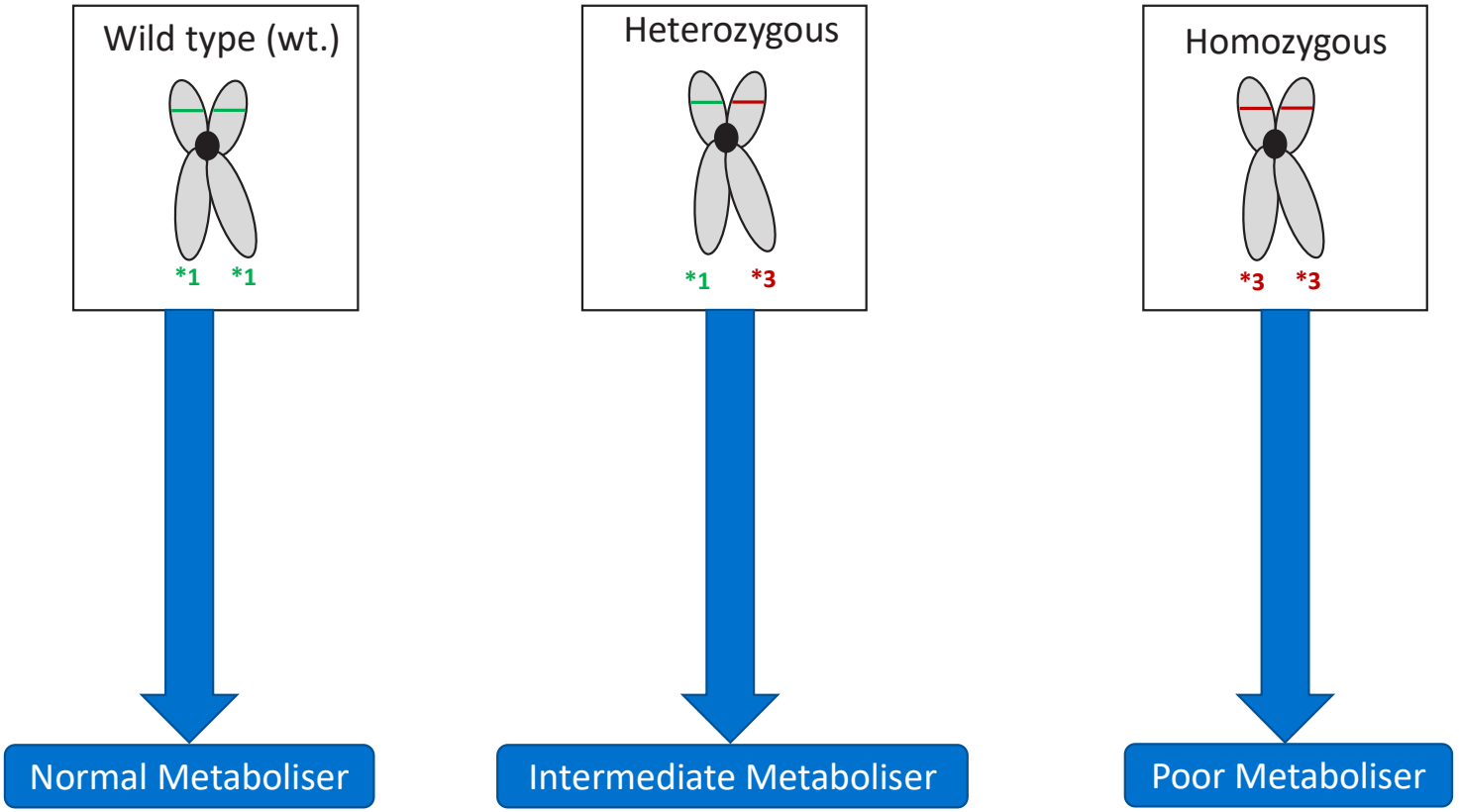
Intermediate Metaboliser

- An individual with one normal function allele PLUS one no function allele

Poor Metaboliser

- An individual with two no function alleles

Linking NUDT15 Genotype and Phenotype



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Why should I test?

Why is it important to test?

TPMT and NUDT15 are key enzymes in the metabolism and inactivation of 6-MP.
Enzyme activity is regulated by common generic polymorphisms; there is substantial evidence linking TPMT/NUDT15 genotype to phenotypic variability[6]

Tolerance and Safety

Genetic variation in *TMPT* and *NUDT15* genes strongly influence tolerance of 6-MP and the safety of 6-MP therapy[2,3]

Identify at risk patients

Testing analyses specific SNP locations in *TPMT* and/or *NUDT15* genes to identify at risk patients

Patients with loss of function variants

↓

Lower or absent enzymatic activity

↓

Cellular accumulation of active metabolites (TGNs)

↓

More likely to experience severe bone marrow suppression

Why is it important to test?

Starting doses of 6-MP can be modified appropriately to prevent severe toxicity for patients

Only ~89% of the population have normal activity levels of TPMT with two wildtype (*1) alleles[6]

89% = normal activity

10-11% of the population have intermediate TPMT activity[6] – heterozygous with one variant allele

>10% = intermediate activity

30-60% of these patients cannot tolerate full dose

~0.3% of European patients are poor metabolisers – homozygous for variant allele(s)

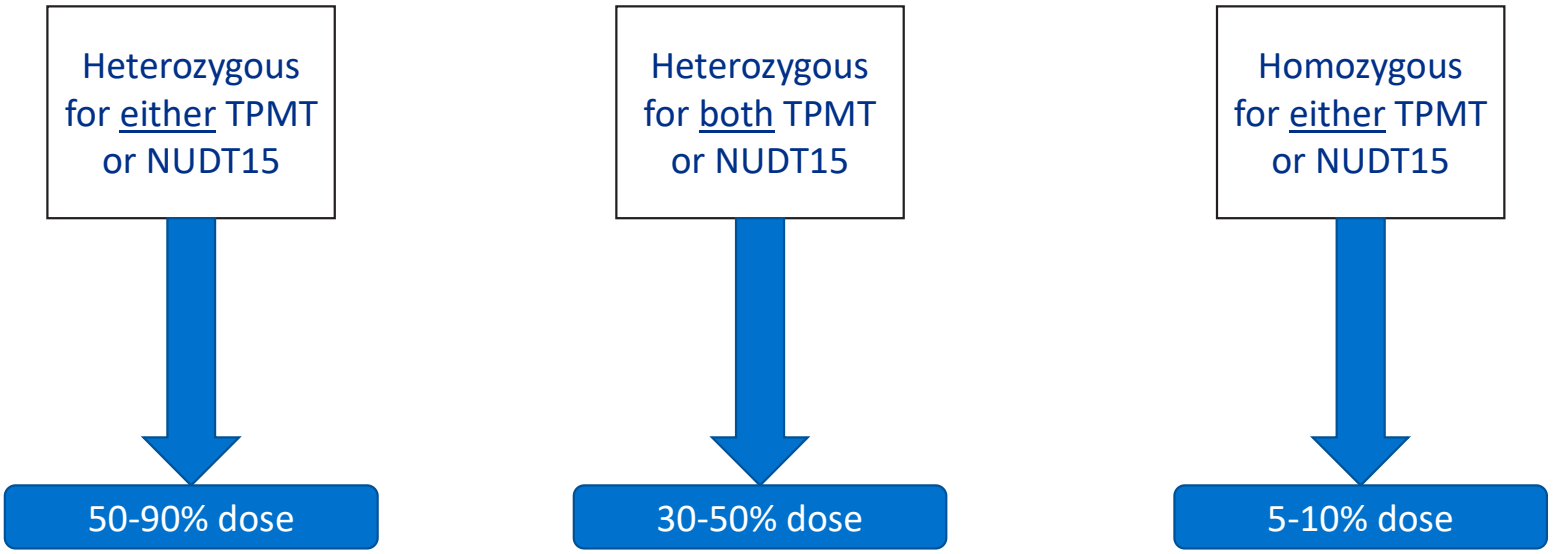
0.3% = little/no activity

Risk severe myelosuppression with full dose 6-MP[7]

Note: starting doses of 6-MP are generally 'high' because doses are derived from trials and weighted by the ~90% of the population who are wildtype (wt.)

Paediatric ALL data

- In a paediatric ALL study (n=1028), the approximated tolerated 6-MP dosage range* for patients with TPMT and/or NUDT15 deficiency was[7]:



Individuals with loss of function allele for both TPMT and NDUT15 likely require more substantial dose reductions

* As a percentage of the planned dosage

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What are the recommendations?

Recommendation

- Adult patients with a confirmed diagnosis of ALL and proposed treatment with 6-MP should be genotyped for the following *TPMT* and *NUDT15* loss of function variants before commencing treatment[2,3]

GENETIC VARIANT		EFFECT
Star (*) Allele	**HGVS cDNA Nomenclature**	**Amino acid substitution**
TPMT		
*Note: TPMT*1 = the normal function allele and normal enzyme activity (wildtype)*		
TPMT*2	c.238 G>C	Ala80Pro
TPMT*3A (most common)	c.460 G>A c.719 A>G	Ala154Thr Tyr240Cys *2 nucleotide transition mutations*
TMPT*3B	c.460 G>A	Ala154Thr
TPMT*3C	c.719 A>G	Tyr240Cys
NUDT15		
NUDT15*3	C415 C>T	Arg139Cys

Pharmacogenetic testing for these recommended variants will not exclude other *TPMT* or *NUDT15* variants that may cause individuals to be intermediate of poor metabolisers of 6-MP

Many factors contribute to an individual's response to a medicine. Additional non-genetic factors i.e. environmental and endogenous factors can affect the translation of phenotype from genotype and must be considered in the clinical context of the patient when applying dose modifications

Recommendation

- **Pharmacogenetic testing for recommended *TPMT* and *NUDT15* variants will not exclude other *TPMT* or *NUDT15* variants that may cause individuals to be intermediate or poor metabolisers**

- As with any targeted genotyping approach, rarer alleles do exists that will not be detected

- Genomic lab reports should specify the variants tested and have a disclaimer that:
  'the test result does not exclude the presence of other TPMT and NUDT15 variants'

- If results are only available for one of the genes, prescribing recommendations based on that result should be implemented with the caveat there is missing information which could have implications

- In the case of missing results or unexpected toxicities, the ethnic distribution of variant alleles should be considered i.e. *NUDT15* variants higher amongst Asian and Hispanic patients and *TPMT* higher amongst European and African patients

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How can I order a test?

Ordering a Test

- Individual organisations should have a clear procedure for requesting *TPMT* and *NUTD15* genotyping
- Testing should be done **at the point of diagnosis** to ensure that the relevant genetic information is available prior to starting 6-MP
- Testing will be done as part of a larger panel test and reported through the SIHMDS network
- Institutions should work with the appropriate testing laboratory to aim for a clinically appropriate turnaround time

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How do I interpret the result?

Clinical interpretation of the result

- Patients who are identified as having one or more loss of function alleles should be considered for 6-MP dose modification based on *TPMT* and/or *NUDT15* genotypes
- Genotype-guided prescribing recommendations apply primarily to **starting** doses
- Subsequent dosing should be guided by monitoring of myelosuppression and response to treatment; if a patient tolerates the dose reduction doses can be titrated
- Clinicians should evaluate markers of disease progression and/or myelosuppression and adjust treatment as necessary according to response and stage of treatment
- If a patient experiences toxicities in the context of a 'normal' TPMT and/or NUDT15 genotyping result, 6-MP should be reduced or held and restarted in line with standard ALL treatment protocols
  - Consider presence of a TPMT/NUDT15 variant that has not been tested for

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Dose Modifications

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Standard Dosing of 6-MP

- Doses of 6-MP in adult ALL protocols are typically **60mg/m^2/day** during induction and consolidation and **75mg/m^2/day** in maintenance
- Doses are slightly lower in protocols for older patients i.e. in UKALL 60+ dosing; 50mg/m^2/day in consolidation and between 25mg m^2/day - 75mg/m^2/day in maintenance
- During maintenance treatment, doses of 6-MP are titrated upwards in 25% dose increments at 4-weekly intervals to maintain ANC 0.75-1.5x10^9/L and Platelets 75-150x10^9/L
- **Note: There is no maximum dose of 6-MP**
- If ANC count falls below 0.75x10^9/L, 6-MP should be reduced by 50%, and if ANC count falls below 0.5x10^9/L 6-MP should be stopped until improves
- Similar adjustments will be made to maintain platelet count between 75-150x10^9/L

Standard Dosing of 6-MP

Response to 6-MP therapy, in terms of marrow suppression, is highly variable

The ability of patients to form active TGN metabolites from the parent pro-drug is important in terms of the disease control and risk of disease relapse

Dose adjustments in the context of neutrophil and platelet levels remain important to ensure that the patient continues to derive maximum benefit from their treatment

TPMT Dose Modifications

- Recommended dosing of 6-MP by TPMT phenotype (assuming NUDT15 phenotype is normal metaboliser)

Genotype	Variant Allele(s)	Diplotype (allele combination)	Likely Phenotype	Recommendation for Dosing of 6-MP
Wild Type (wt.)	None	*TPMT* *1/*1	Normal metaboliser	Standard doses of 6-MP (previous slide)
Heterozygous	c.238 G>C	*TPMT* *1/*2	Intermediate metaboliser	Starting doses should not exceed 60mg/m^2/day in any treatment phase. If tolerated, can increase dose in 25% increments after minimum 2-week intervals Generally tolerate a dose of 50-60mg/m^2/day.
	c.460 G>A, c.719 A>G	*TPMT* *1/*3A		
	c.460 G>A	*TPMT* *1/*3B		
	c.719 A>G	*TPMT* *1/*3C		
Homozygous	c.238 G>C	*TPMT* *2/*2	Poor metaboliser (High risk of myelosuppression)	Commence dosing at 5mg/m^2/day. If tolerated, can increase dose in 10% increments after minimum 4-week intervals
	c.460 G>A, c.719 A>G	*TPMT* *3A/*3A		
	c.460 G>A	*TPMT* *3B/*3B		
	c.719 A>G	*TPMT* *3C/*3C		
Compound Heterozygous	c.238 G>C; c.460 G>A, c.719 A>G	*TPMT* *2/*3A		
	c.238 G>C; c.460 G>A	*TPMT* *2/*3B		
	c.238 G>C; c.719 A>G	*TPMT* *2/*3C		
	c.460 G>A, c.719 A>G; c.460 G>A	*TPMT* *3A/*3B		
	c.460 G>A, c.719 A>G; c.719 A>G	*TPMT* *3A/*3C		
	c.460 G>A; c.719 A>G	*TPMT* *3B/*3C		

NUDT15 Dose Modifications

- Recommended dosing of 6-MP by *NUDT15* phenotype (assuming *TPMT* phenotype is normal metaboliser)

Genotype	Variant Allele(s)	Diplotype	Likely Phenotype	Recommendation for Dosing of 6-MP
Wild Type (wt.)	None	*NUDT15* *1/*1	Normal metaboliser	Standard doses of 6-MP
Heterozygous	c.415 C>T	*NUDT15* *1/*3	Intermediate metaboliser	Starting doses should not exceed 60mg/m^2/day in any treatment phase. If tolerated, can increase dose in 25% increments after minimum 2-week intervals Generally tolerate a dose of 50-60mg/m^2/day.
Homozygous	c.415 C>T	*NUDT15* *3/*3	Poor metaboliser (High risk of myelosuppression)	Commence dosing at 5mg/m^2/day. If tolerated, can increase dose in 10% increments after minimum 4-week intervals

TPMT and NUDT15 Combination Phenotypes

- Recommended dosing of 6-MP for individuals with a combination phenotype

TPMT Likely Phenotype	NUDT15 Likely Phenotype	Recommendation for Dosing of 6-MP
Intermediate metaboliser	Intermediate metaboliser	Commence dosing at 5mg/m^2/day. If tolerated, can increase dose in 10% increments after minimum 4-week intervals
Intermediate metaboliser	Poor metaboliser	
Poor metaboliser	Intermediate metaboliser	
Poor metaboliser	Poor metaboliser	

- Note: the two genes are independent and the likelihood of an individual being an intermediate or poor metaboliser for both relies on the population frequencies for the different variant alleles

Phenotype vs Genotype testing

- TPMT activity may also be tested using an enzyme activity assay (phenotyping assay); this will directly measure the TPMT enzyme activity in red blood cells (RBCs)
- There is no clinically available assay for NUDT15 enzyme activity

ADVANTAGE:

- Identify individuals with low TPMT activity due to rare variant alleles not currently recommended for testing

BUT, in leukaemia patients:

- Concordance between TPMT phenotype and genotype is poor due to[7]:

Greatly reduced red cell TPMT activity due to atypical haematopoiesis as a result of the disease	Anaemia associated with ALL due to deficient RBC production and an excess of relatively older RBCs circulating	Receiving chemotherapy; can cause a higher level of TPMT activity likely due to an excess of young, immature RBCs which inherently have higher TPMT activity

- Phenotype testing may also not be accurate in patient who have recent had a blood transfusion
- ***To avoid an incorrect TPMT status being recorded, genotype testing is recommended for leukaemia patients***

Summary

- TPMT and NUDT15 act as negative modulators of both 6-MP activation and 6-MP toxicity:
  - TPMT metabolises 6-MP to an inactive methyl-mercaptopurine base
    lack of TPMT activity = reduced inactivation of 6-MP and therefore increased toxic effect
  - NUDT15 dephosphorylates active TGN metabolites to prevent their incorporation into DNA:
    lack of NUDT15 activity = more TGNs available, increased DNA damage and cell death
- The activity of these enzymes is influenced by genetic variability in *TPMT* and *NUDT15* genes
- *TMPT* and *NUDT15* variant alleles are associated with decreased or absent enzymatic activity which is a major contributor to 6-MP induced myelosuppression
- Patients with one or more of these variant alleles are at increased risk of toxicity and risk of severe myelosuppression with normal 6-MP doses

Summary of Recommendations

- ***TPMT and NUDT15 genotype testing should be considered for all patients treated with 6-MP***
- Testing can identify individuals at increased risk of myelosuppression to allow dose modifications without compromising disease control
- The alleles suggested for testing are the most common variants in most populations but testing will not pick up rarer variants
- Presence of a rare variant must always be considered in the event of severe toxicity in the context of a 'normal' TPMT and/or NUDT15 level

Learning Objectives Check

- ✓ Understand what acute lymphoblastic leukemia (ALL) is and the underlying patho-physiology of the disease
- ✓ Describe the role of 6-mercaptopurine in ALL treatment and understand its mechanism of action
- ✓ Understand the role of TPMT and NUDT15 in the metabolism and detoxification of 6-mercaptopurine
- ✓ Identify the common variant alleles that contribute to reduced or absent enzymatic activity and link this to increased risk of toxicity
- ✓ Understand the importance of genetic testing in patients receiving 6-mercaptopurine and be able to implement dose modifications according to a patients phenotype

References

1. Cancer Research UK (2021) *What is acute lymphoblastic leukemia (ALL).* Available at: https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about (Accessed 16th March 2023)

2. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ. (2019) 'Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update'. *Clin Pharmacol Ther*, 105(5):1095-1105

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Case Study

Hosted by UCLPartners

Mrs MK

- 50y old female, diagnosed with B-ALL January 2022
- Admitted to hospital with pancytopenia
  - Hb 66, WCC 144, Neutrophils 0.7, Platelets 39
- Completed induction cycle 1 as per the UKALL 14 protocol (standard treatment for patients aged 25-65h) and has count recovered
- Due to start induction cycle 2 which contains 6-MP 60mg/m^2 OD for 28 days

Scenario 1: no genotyping result

- You check on her health record and there is no TPMT/NUDT15 genotyping.
- You request this urgently but are told the turnaround time is up to 1 week
- What do you do?
  - (a) Proceed with 6-MP at a dose of 60mg/m^2 OD and amend dose if needed when the result comes back
  - (b) Delay starting induction phase 2 until you have a genotype result
  - (c) Proceed with a reduced dose of 6-MP and if so, what dose do you choose?

**TO FINISH: we would like reduce the dose as if they were deficient and proceed but want to get a general consensus. Likely a discussion between (b) and (c)

Scenario 2: TPMT deficiency

- You check on her health record and there is a TPMT genotype result:

TPMT *1/*3C

Q1. What phenotype does this genotype confer?

She is heterozygous for 1 wt. allele and 1 loss of function variant allele
Intermediate metaboliser

Q2. What does this mean in terms of her TPMT enzyme activity

She has reduced TPMT enzyme activity and therefore at risk of increased myelosuppession with standard doses of 6-MP

Q3. What starting dose would you recommend?

Starting dose should not exceed 60mg/m^2/day in any treatment phase
These patients usually tolerate a dose of 50-60mg/m^2/day
Likely start at 50mg/m^2/day

- She is then reviewed and has experienced no myelosuppression – do you amend her dose?

Dose tolerated can increase dose
Dose increases should be in 25% increments after minimum 2-week intervals

Scenario 3: TPMT deficiency

- You check on her health record and there is a TPMT genotype result:

TPMT *2/*3C

Q1. What phenotype does this genotype confer?

She is compound heterozygous for 2 different loss of function variant alleles
Poor metaboliser

Q2. What does this mean in terms of her TPMT enzyme activity

She has little or no TPMT enzyme activity and therefore at high risk of increased myelosuppession with standard doses of 6-MP

Q3. What starting dose would you recommend?

Starting dose 5mg/m^2/day

- She is reviewed and has experienced no myelosuppression - do you amend her dose?

Dose tolerated can increase dose
Dose increases should be in 10% increments after minimum 4-week intervals

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Thank you!

For more information please contact:

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