Dear Colleague,

Report comments for *DPYD* pharmacogenomic testing

Please find below report comments (updated 29nd December 2020) for variant DPYD genotypes associated with fluoropyrimidine toxicity. The comments are consistent with UK Chemotherapy Board July 2020 fluoropyrimidine dose adjustment guidance for patients with variant *DPYD* genotypes.

WILDTYPE

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

No DPYD variants were found. DPD deficiency is unlikely to be a cause of severe toxicity to fluoropyrimidine therapy. However, the presence of a rare variant which could cause toxicity cannot be excluded.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Heterozygous DPYD c.1905+1G>A

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is heterozygous for the variant DPYD c.1905+1G>A. A heterozygous genotype is associated with partial DPD deficiency and severe toxicity to fluoropyrimidine therapy at standard doses.

Consider a 50% dose reduction or alternative therapy. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Heterozygous c.2846A>T p.(Asp949Val)

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

The patient is heterozygous for the variant DPYD c.2846A>T p.(Asp949Val). A heterozygous genotype is associated with partial DPD deficiency and severe toxicity to fluoropyrimidine therapy at standard doses.

Consider a 50% dose reduction. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles. If no toxicity is observed at a dose of 75%, a further increment to a maximum of 85% may be possible, but caution is advised.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Heterozygous c.1679T>G p.(Ile560Ser).

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is heterozygous for the variant DPYD c.1679T>G p.(Ile560Ser). A heterozygous genotype is associated with partial DPD deficiency and severe toxicity to fluoropyrimidine therapy at standard doses.

Consider a 50% dose reduction or alternative therapy. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Heterozygous c.1236G>A/HapB3

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

The patient is heterozygous for the variant DPYD c.1236G>A/HapB3. A heterozygous genotype is associated with partial DPD deficiency and severe toxicity to fluoropyrimidine therapy at standard doses.

Consider a 50% dose reduction. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles. If no toxicity is observed at a dose of 75%, a further increment to a maximum of 85% may be possible, but caution is advised.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Homozygous and compound heterozygous genotypes

c.1236G>A/HapB3 / c.1905+1G>A

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is compound heterozygous for the variants DPYD c.1905+1G>A and c.1236G>A/HapB3.

Consider alternate therapy (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider a starting dose of 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 25% of the target dose.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

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c.2846A>T / c.1905+1G>A

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is compound heterozygous for the variants DPYD c.1905+1G>A and c.2846A>T p.(Asp949Val).

Consider alternate therapy (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider a starting dose of 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 25% of the target dose.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

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c.1236G>A/HapB3 and c.2846A>T

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is compound heterozygous for the variants DPYD c.1236G>A/HapB3 and c.2846A>T p.(Asp949Val).

Consider alternate therapy (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 50% of the target dose.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

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c.2846A>T p.(Asp949Val) HOMOZYGOUS

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is homozygous for the variant DPYD c.2846A>T p.Asp949Val).

Consider alternate therapy (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 50% of the target dose.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

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c.1236G>A/HapB3 HOMOZYGOUS

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is homozygous for the variant DPYD c.1236G>A/HapB3.

Consider alternate therapy (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 50% of the target dose.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays.

Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

c.1905+1G>A HOMOZYGOUS

DPYD VARIANT ANALYSIS – FLUOROPYRIMIDINE TOXICITY

CAUTION: HIGH RISK OF FATAL TOXICITY. The patient is homozygous for the variant DPYD c.1905+1G>A. A homozygous genotype is associated with complete DPD deficiency and extremely severe, usually fatal toxicity to fluoropyrimidine therapy.

Do not use fluoropyrimidine therapy. Consider raltitrexed or trifluridine/tipiracil.

The patient was genotyped for the DPYD variants c.1679T>G p.(Ile560Ser), c.1905+1G>A, c.2846A>T p.(Asp949Val) and c.1236G>A/HapB3 p.(Glu412=) by TaqMan genotyping assays. Reference sequence NM_000110.4. Dosing guidance reference: UK Chemotherapy Board Personalised Medicine Approach For Fluoropyrimidine-based Therapies, July 2020.

Our contact details:

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Yours sincerely

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