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Notification of changes to *DYPD* testing from 22nd September 2025

Dear Colleague,

We are making some improvements to our routine *DPYD* testing at the NWGLH (Liverpool site) and this letter provides details of the forthcoming changes.

The laboratory has previously provided testing for four *DPYD* variants associated with partial DPD deficiency and severe toxicity to fluorouracil-based drugs:

- c.1905+1G>A
- c.1679T>G p.(Ile560Ser)
- c.2846A>T p.(Asp949Val)
- c.1236G>A p.(Glu412=) – used as a proxy to infer the presence of the reduced function c.1129-5923C>G variant, as the two variants are commonly inherited together.

From Monday 22nd September, the laboratory will be testing directly for the *DPYD* c.1129-5923C>G variant and introducing testing of a fifth *DPYD* variant c.557A>G p(Tyr186Cys). Testing for the c.1905+1G>A, c.1679T>G p.(Ile560Ser) and c.2846A>T p.(Asp949Val) variants will remain unchanged.

These changes are being implemented due to anticipated updated guidance in the NHS England National Genomic Test Directory (likely to be formalised in October 2025). The rationale for the changes is as follows:

- **Direct testing of the *DYPD* c.1129-5923C>G variant replacing c.1236G>A proxy testing:**
  Recent evidence has shown that c.1236G>A and c.1129-5923C>G are not inherited together in all patients. As such, c.1236G>A should not be used as a proxy to infer the presence of the c.1129-5923C>G reduced function variant, and direct testing for c.1129-5923C>G is now recommended (CPIC Guideline for Fluoropyrimidines and DPYD. January 2024 update (edited March 2024). Accessed at https://cpicpgx.org/guidelines/guideline-forfluoropyrimidines-and-dpyd/).

- **Introduction of *DPYD* c.557A>G p(Tyr186Cys) variant testing:**
  c.557A>G p.(Tyr186Cys) is a decreased function variant found in approximately 2% of individuals of African ancestry. Given the variant's high frequency, Chan et al. (2024) (PMID: 38886557) recommend its inclusion in routine testing.

The laboratory has validated two new testing kits (manufactured by LaCAR MDx Technologies, Liège, Belgium) to incorporate these changes into the laboratory's routine service provision for *DPYD*.

The target turnaround time of five calendar days for *DPYD* referrals is not impacted by these changes.

Please do not hesitate to contact us if you have any queries.

Yours sincerely,

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