

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between TPMT/NUDT15 and thiopurines.

Title: Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between TPMT/NUDT15 and thiopurines.

Publication year: 2026

Journal: European journal of human genetics : EJHG

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Society: Dutch Pharmacogenetics Working Group

Origin country: Netherlands

DOI: 10.1038/s41431-025-01986-8

PMID: 41318725

Source: <https://pubmed.ncbi.nlm.nih.gov/41318725/>

Eur J Hum Genet Eur J Hum Genet 1300 ejhg 9302235 European Journal of Human Genetics 1018-4813 1476-5438 Nature Publishing Group PMC12816135 PMC12816135.1 12816135 12816135 41318725 10.1038/s41431-025-01986-8 1986 1 Article Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between TPMT / NUDT15 and thiopurines <http://orcid.org/0000-0001-8796-2031> Coenen Marieke J. H. 1 <http://orcid.org/0000-0001-7476-6867> Nijenhuis Marga M. Nijenhuis@knmp.nl 2 Soree Bianca 2 de Boer-Veger Nienke J. 3 Buunk Anne Marie 4 Guchelaar Henk-Jan 5 <http://orcid.org/0000-0002-9927-7266> Houwink Elisa J. F. 6 7 Risselada Arne 8 Rongen Gerard A. P. J. M. 9 10 <http://orcid.org/0000-0002-3965-5552> Swen Jesse J. 5 <http://orcid.org/0000-0002-1429-4789> Touw Daan J. 11 <http://orcid.org/0000-0003-2298-9924> van Westrhenen Roos 12 13 14 Deneer Vera H. M. 15 16 van Schaik Ron H. N. 1 1 <https://ror.org/018906e22> grid.5645.2 0000 0004 0459 992X Department of Clinical Chemistry, Erasmus MC University Medical Center, Rotterdam, The Netherlands 2 <https://ror.org/00gdw7f12> grid.489189.5 0000 0001 0708 7338 Royal Dutch Pharmacists Association (KNMP), The Hague, The Netherlands 3 <https://ror.org/017b69w10> grid.416468.9 0000 0004 0631 9063 Department of Clinical Pharmacy, Martini Hospital, Groningen, The Netherlands 4 Pharmacy De Katwijkse Apotheek, Katwijk, The Netherlands 5 <https://ror.org/05xvt9f17> grid.10419.3d 0000000089452978 Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands 6 <https://ror.org/02qp3tb03> grid.66875.3a 0000 0004 0459 167X Department of Family Medicine, Public Health and Primary Care (PHEG), Mayo Clinic, Rochester, MN USA 7 <https://ror.org/05xvt9f17> grid.10419.3d 0000000089452978 Department of Public Health and Primary Care (PHEG), Leiden University Medical Center, Leiden, the Netherlands 8 Department of Clinical Pharmacy, Wilhelmina Hospital, Assen, The Netherlands 9 <https://ror.org/05wg1m734> grid.10417.33 0000 0004 0444 9382 Department of Internal Medicine, Radboud university medical center, Nijmegen, The Netherlands 10 <https://ror.org/05wg1m734> grid.10417.33 0000 0004 0444 9382 Department of Pharmacology and Toxicology, Radboud university medical center, Nijmegen, The Netherlands 11 <https://ror.org/03cv38k47> grid.4494.d 0000 0000 9558 4598 Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, Groningen, The Netherlands 12 <https://ror.org/002wh3v03> grid.476585.d 0000 0004 0447 7260 Department of Psychiatry, Parnassia Group, Amsterdam, The Netherlands 13 <https://ror.org/0220mzb33> grid.13097.3c 0000 0001 2322 6764 Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, UK 14 <https://ror.org/03qvjzj64> grid.482756.a St. John's National Academy of Health Sciences, Bengaluru, India 15 <https://ror.org/04pp8hn57> grid.5477.1 0000 0000 9637 0671 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands 16 <https://ror.org/0575yy874> grid.7692.a 0000 0000 9012 6352 Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics,

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2025 The Dutch Pharmacogenetics Working Group (DPWG) describes gene-drug interactions to
facilitate pharmacogenetic implementation in clinical practice. The current guideline describes the
gene-drug interactions for TPMT, NUDT15 and thiopurines (azathioprine, 6-mercaptopurine and
thioguanine). Evidence based recommendations were obtained via a literature review of published
studies. This literature review showed that gene variants leading to a decreased activity of TPMT
and/or NUDT15 result in higher risk of toxicities, especially bone-marrow depression. For
intermediate metabolisers (IM) of TPMT or NUDT15, it is advised to start with 50% of the normal
dose when treated with azathioprine or 6-mercaptopurine. For poor metabolisers (PM), it is advised
to start with an alternative treatment or to reduce the dose to 10% of the normal dose. For
thioguanine, a dose of 75% of the normal dose is advised for TPMT IM and 50% of the normal dose
for NUDT15 IM. Alternative treatment or a start dose reduction is advised for PM. A start dose of
6-7% can be used for TPMT PM and of 10% for NUDT15 PM. For TPMT or NUDT15 IM treated for
leukaemia, starting with the normal dose can be considered and then decrease the dose to the
advised dose described above in case toxicities occur. For NUDT15 PM reduced starting dose is
advised only if an alternative is not possible, due to a higher uncertainty in the calculated dose
reduction for NUDT15 PM than for TPMT PM.

DPWG classifies genotyping for TPMT and NUDT15 "essential" before thiopurine initiation.