ABCG2: allopurinol 7255/7256

ABCG2 = ATP Binding Cassette Transporter, Subfamily G, Member 2, BMI = body-mass index, CI = confidence interval, CTCAE = common terminology criteria for adverse events, eGFR = estimated glomerular filtration rate, OR = odds ratio, OR_{adj} = adjusted odds ratio, NS = non-significant, S = significant, SmPC = Summary of Product Characteristics, SNP = single nucleotide polymorphism, 141KK = 141LysLys = homozygous variant allele (strongly reduced transporter activity) = rs2231142AA = rs2231142TT, 141QK = 141GlnLys = heterozygous (reduced transporter activity) = rs2231142CA = rs2231142GT, 141QQ = 141GlnGln = homozygous wild-type allele (normal transporter activity) = rs2231142CC = rs2231142GG.

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Allopurinol is rapidly converted in the body to the active metabolite oxypurinol, which is responsible for most of the uric acid lowering effect. Allopurinol and oxypurinol lower uric acid by diminishing the uric acid production. They inhibit the enzyme xanthine oxidase, that degrades hypoxanthine and xanthine into uric acid.
The ATP Binding Cassette Transporter, Subfamily G, Member 2 (ABCG2) is an efflux transporter playing an important role in excretion of uric acid into the kidneys and intestinal tract. In addition, oxypurinol has been reported to be a substrate of ABCG2. Because of this, gene variants resulting in diminished efflux transporter activity might both increase the serum uric acid concentration and influence the effectiveness of allopurinol in lowering this concentration.
ABCG2 is an uric acid efflux transporter and reports suggest an association between ABCG2 Q141K and hyperuricemia and gout, resulting in a higher frequency of the 141K-allel in hyperuricemic patients, so in patients with an indication for allopurinol.
Gene variant Q141K:
Five of the eight studies (Stamp 2020, Brackman 2019, Wright 2018, Wallace 2018, and Roberts 2017) and a case-report (Petru 2016) showed a decreased effectiveness of allopurinol in carriers of 141K. Of these five studies, two investigated the same group of patients (Stamp 2020 and Wright 2018) and one (Brackman 2019) was an extension of a study not showing a significant effect of the 141K allele (Wen 2015).
Because of the decreased effectiveness, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction and that adjustment of therapy is recommended (yes/yes-interactions). The KNMP Pharmacogenetics Working Group recommends to use a higher allopurinol dose in patients with the 141QK and 141KK phenotypes. Because only Wright 2018 provided data on the required allopurinol dose for the different Q141K phenotypes, the required increase in allopurinol dose mentioned in the recommendation was derived from this study (a 1.25 fold higher dose for 141QK and a 1.4 fold higher dose for 141KK).
An overview of the clinical and kinetic effects per phenotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background text via your pharmacy or physician electronic decision support system.
Gene variant rs10011796:
A genome wide association study found a decreased effectiveness of allopurinol in non-Hispanic White carriers of the rs10011796 variant allele, but not in carriers of all ethnicities (Wen 2015). Roberts 2017 did not find an effect of rs10011796 on the effectiveness of allopurinol. Wallace 2018 found an effect, but significance disappeared after adjustment for Q141K, indicating that Q141K instead of rs10011796 was the cause for the decreased effectiveness of allopurinol. .
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was insufficient evidence for a clinically relevant effect of this gene variant on ABCG2 transporter activity and thus, no cause for inclusion of this gene variant in the ABCG2 pharmacogenetic interactions.
Gene variants rs11732936, rs2725271, rs3114020, rs4148155, and rs74904971:
No effect on allopurinol effectiveness was found for any of these gene variants (Wen 2015).
Because of the lack of evidence for a clinically relevant effect of these gene variants on ABCG2 transporter activity, the KNMP Pharmacogenetics Working Group decided that there was no cause for inclusion of these gene variants in the ABCG2 pharmacogenetic interactions.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping of ABCG2 before starting allopurinol to be potentially beneficial for drug effectiveness. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
A case report showed ineffectiveness of allopurinol in decreasing the serum uric acid concentration to result in development of severe chronic tophaceous gout, requiring repeated surgical intervention, and uric acid nephropathy in a male patient with partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency that results in uric acid overproduction. The severity of this negative clinical effect is code D corresponding to CTCAE grade 3. This results in a score of 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE Grade 3 or 4).
There were no studies confirming a clinical effect grade ≥ 3. All studies investigated only serum uric acid concentrations and not possible clinical consequences of inadequate serum uric acid lowering by allopurinol. The absence of supporting studies results in a score of 0 of the maximum of 3 points for the second criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one supporting study).
Because a clinical effect grade ≥ 3 is only reported in a case report, there are no indications that the number needed to genotype (NNG) to prevent one clinical effect grade ≥ 3 is smaller than 1000. For this reason, this results in a score of 0 of the maximum of 3 points for the third criterion of the clinical implication score: the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The Summary of Product Characteristics (SmPC) of allopurinol does not mention the ABCG2 141QK or 141KK phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

The table below follows KNMP nomenclature for ABCG2 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Stamp LK et al. Relationships between allopurinol dose, oxypurinol concentration and urate-lowering response - in search of a minimum effective oxypurinol concentration. Clin Transl Sci 2020;13:110-5. PMID: 31444839.</td>
<td>3

141KK: A

141QK: A</td>
<td>In 129 gout patients from the dose escalation study of Wright 2018, sensitivity to allopurinol (defined as the change in plasma urate for each 100 mg increase in allopurinol dose) was determined. In addition, the change in plasma oxypurinol for each 100 mg increase in allopurinol was measured.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded.
Multivariate analysis adjusting for creatinine clearance, body mass index, and baseline urate was performed.

Genotyping:
- 74x 141QQ
- 44x 141QK
- 11x 141KK

Results:
<table>
<tr><td colspan="2">Results for 141KK versus 141QK versus 141QQ:</td></tr>
<tr><td>allopurinol sensitivity</td><td>decrease with increasing number of variant alleles (S)</td></tr>
<tr><td></td><td>The value for 141QQ was a decrease in plasma urate of approximately 0.065 mmol/L (1.1 mg/dL) for each 100 mg increase in allopurinol. For 141QK and 141KK, this was approximately 0.8x and 0.4x the value for 141QQ, respectively. 141KK was an independent predictor of allopurinol sensitivity (S).</td></tr>
<tr><td>plasma oxypurinol</td><td>decrease with increasing number of variant</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Other variables, including ABCG2 Q141K genotype, impact on sensitivity to allopurinol.”</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td><table><tr><td>increase for each 100 mg increase in allopurinol</td><td>alleles (S)
141KK was an independent predictor of plasma oxypurinol increase (S).</td></tr></table></td><td></td></tr>
<tr><td>ref. 2
Brackman DJ et al.
Genome-wide association and functional studies reveal novel pharmacological mechanisms for allopurinol.
Clin Pharmacol Ther 2019;106:623-31.
PMID: 30924126.</td><td>3

141KK: A

141QK: A</td><td>A genome-wide association study for allopurinol response was performed after expansion of the cohort of Wen 2015 to a total of 3179 patients, including 2647 non-Hispanic Whites, 303 Asians, 115 African Americans, and 114 Hispanics. Two independent cohorts with 601 and 328 patients respectively were used to validate the results. The effect of Q141K on complete response (all serum uric acid concentrations measured after treatment start below the recommended 0.36 mmol/L) was determined in 1316 non-Hispanic White patients by logistic regression analysis adjusting for baseline serum uric acid, gender and dose.
Nonadherence accounted for using prescription refills and by only allowing subjects included in the analysis to go one week in between prescriptions. The mean allopurinol dose in all cohorts was approximately 200 mg/day.
The major outcome assessed in this study was initial uricemic response to allopurinol, which was defined as the change in serum uric acid (treated - untreated) at the first follow-up appointment.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded.

Results:<table><tr><td colspan="3">Associations with allopurinol response:</td></tr><tr><td rowspan="5">genome wide association study of allopurinol response (decrease in serum uric acid concentration)</td><td rowspan="3">non-Hispanic Whites</td><td>The strongest association with worse response to allopurinol was found for rs45499402, which is in perfect linkage disequilibrium with Q141K (S).</td></tr><tr><td>Conditional analysis, which included Q141K as a covariate, reduced the P value of the next strongest association within the ABCG2 locus to P = 0.03, suggesting that either Q141K or an SNP in high linkage disequilibrium is the causal SNP for the association with worse response to allopurinol.</td></tr><tr><td>Note: In a figure showing the allopurinol response for each Q141K-phenotype for different doses, the decrease in response with increasing number of 141K alleles was visible for allopurinol 100 mg/day, but not for 200, 300 and 600 mg/day.</td></tr><tr><td rowspan="2">all ethnicities</td><td>A strong association with worse response to allopurinol was found for Q141K (S).</td></tr><tr><td>A stronger association with worse response to allopurinol was found for Q141K after expansion of the cohort with the two independent replication cohorts (S).</td></tr><tr><td colspan="2">% of non-Hispanic Whites with complete response (all serum uric acid concentrations determined after treatment start < 0.36 mmol/L)</td><td>141QK+141KK versus 141QQ: OR = 0.71 (S)</td></tr></table>Note: In this cohort, Q141K does not associate with baseline serum uric acid concentration at genome-wide significance (NS).</td><td>Author’s conclusion:
”These results provide strong evidence for a role of BCRP Q141K in allopurinol response, and suggest that allopurinol may have additional hypouricemic effects beyond xanthine oxidase inhibition.”</td></tr>
</table>

<table>
<tr>
<td>ref. 3
Zhang K et al.
ABCG2 gene polymorphism rs2231142 is associated with gout comorbidities but not allopurinol response in primary gout patients of a Chinese Han male population.
Hereditas 2019;156:26.
PMID: 31367212.</td>
<td>3

141KK: AA

141QK: AA</td>
<td>642 gout patients, treated with allopurinol, could be classified as good or poor responders. 369 of these patients (57%) were good responders (serum uric acid <0.36 mmol/L on allopurinol ≤300 mg/day)) and the other 273 patients were poor responders (serum uric acid ≥0.36 mmol/L despite allopurinol >300 mg/day).
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded.
Linear regression was conducted to assess associations of variables with therapeutic effect of allopurinol.

Genotyping:
- 165x 141QQ
- 309x 141QK
- 168x 141KK

Results:
<table>
<tr><td colspan="2">Result for 141KK versus 141QK versus 141QQ:</td></tr>
<tr><td rowspan="2">% of patients with poor response</td><td>NS</td></tr>
<tr><td>The result was also NS for 141KK compared to 141QQ.</td></tr>
</table>
Note: In an extended version of this cohort (1205 gout patients), Q141K was associated with baseline serum uric acid concentration and serum creatinine concentration with the values being highest for 141KK (S). In addition, Q141K was associated with nephrolithiasis with the frequency being lowest for 141KK and with chronic kidney disease with the frequency being highest for 141KK (S).</td>
<td>Author’s conclusion:
”ABCG2 rs2231142 may predict the risk of kidney comorbidities for Chinese Han male gout patients, but not allopurinol response.”</td>
</tr>
<tr>
<td>ref. 4
Torres RJ et al.
GLUT9 influences uric acid concentration in patients with Lesch-Nyhan disease.
Int J Rheum Dis 2018;21:1270-6.
PMID: 29879316.</td>
<td>3

141QK: AA</td>
<td>27 patients with hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency that results in uric acid overproduction, were treated with allopurinol for at least 5 years. To prevent xanthine lithiasis due to allopurinol inhibition of xanthineoxidase, allopurinol was titrated to a serum uric acid concentration of 0.258-0.446 mmol/L, with urine xanthine levels < 350 mmol/mol creatinine. The allopurinol dose was 1.16-6.25 mg/kg per day (mean 3.08 mg/kg per day). Serum uric acid after treatment varied from 0.280 to 0.458 mmol/L. Serum uric acid before treatment varied from 0.351 to 1.036 mmol/L.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded.

Genotyping:
- 22x 141QQ
- 5x 141QK

Results:
<table>
<tr><td colspan="3">Result for 141QK compared to 141QQ:</td></tr>
<tr><td></td><td></td><td>value for 141QQ</td></tr>
<tr><td>allopurinol dose</td><td>NS</td><td>3.01 mg/kg</td></tr>
<tr><td>serum uric acid after treatment</td><td>NS</td><td>0.390 mmol/L</td></tr>
<tr><td>serum uric acid before treatment</td><td>NS</td><td>0.627 mmol/L</td></tr>
<tr><td>serum creatinine after treatment</td><td>NS</td><td>0.9 mg/dl</td></tr>
</table>
Note: In an previous study, the authors showed an association of Q141K with gout in persons from the same area (104 gout patients and 300 controls).</td>
<td>Author’s conclusion:
”No relationship between rs2231142 in the ABCG2 gene or rs11231825 in the URAT1 gene and serum urate levels or allopurinol response was found in our patients with HPRT deficiency.”</td>
</tr>
<tr>
<td>ref. 5
Wright DFB et al.
The impact of diuretic use and ABCG2 genotype on the predictive</td>
<td>3</td>
<td>In 142 gout patients with a mean serum uric acid concentration of 0.43 mmol/L on a mean allopurinol dose of 256 mg/day, the allopurinol dose was either escalated during a 24-month period, or kept constant during 12 months, followed by escalation during a 12-month period. Allopurinol dose was increased monthly with 50 mg for those with creatinine clearance ≤ 60 mL/minute and with 100 mg for those with creatinine clearance > 60 mL/minute until the serum uric acid concentration was 0.36 mmol/L.</td>
<td>Author’s conclusion:
”Inclusion of ABCG2 genotype and a revised adjustment for diuretics would further improve</td>
</tr>
</table>

<table>
<tr>
<td>performance of a published allopurinol dosing tool. Br J Clin Pharmacol 2018;84:937-43. PMID: 29341237.

ref. 5, continuation</td>
<td>141KK: A

141QK: A</td>
<td>Patients with plasma oxypurinol <20 µmol/L were considered to be nonadherent with allopurinol and excluded from the analysis. One patient with an implausible dose–response relationship was also excluded (assumed nonadherence).
The dose required to achieve serum uric acid 0.36 mmol/L on two consecutive visits was determined and compared to the dose predicted by an allopurinol dosing model based on renal function, weight and diuretic use.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded. 38% of patients used diuretics.

Genotyping:
- 80x 141QQ
- 49x 141QK
- 13x 141KK

Results:
<table>
<tr><td colspan="5">Results for 141KK versus 141QK versus 141QQ:</td></tr>
<tr><td colspan="2"></td><td>141KK</td><td>141QK</td><td>value for 141QQ</td></tr>
<tr><td rowspan="4">required allopurinol daily dose</td><td>all</td><td>x 1.40 (S)</td><td>x 1.24 (S)</td><td>344 mg</td></tr>
<tr><td>no diuretics</td><td>x 1.39 (NS)</td><td>x 1.19 (NS)</td><td>351 mg</td></tr>
<tr><td>diuretics</td><td>x 1.38 (NS)</td><td>x 1.33 (NS)</td><td>335 mg</td></tr>
<tr><td></td><td colspan="3">Statistical testing was only performed for all patients, not for the subgroups ‘no diuretics’ and ‘diuretics’.</td></tr>
<tr><td rowspan="4">difference in allopurinol dose predicted based on renal function, diuretic use and weight and observed dose</td><td>all</td><td>x 0.07 (S)</td><td>x 0.53 (S)</td><td>201 mg</td></tr>
<tr><td>no diuretics</td><td>x -0.69 (S)</td><td>x 0.57 (S)</td><td>97 mg</td></tr>
<tr><td>diuretics</td><td>x 0.61 (S)</td><td>x 0.72 (S)</td><td>329 mg</td></tr>
<tr><td></td><td colspan="3">Multilinear regression analysis showed the ABCG2 phenotype to be an independent predictor of the difference and thus of the required allopurinol dose, with the 141QQ phenotype overpredicting the dose (i.e. diminishing the observed dose requirement) by 94 mg/day (S). This suggests that adjustment for the ABCG2 phenotype should significantly improve the predictive performance of the model-based dosing tool.</td></tr>
</table></td>
<td>the performance of the dosing tool.”

Required allopurinol dose compared to 141QQ:
141QK: 124%
141KK: 140%</td>
</tr>
<tr>
<td>ref. 6
Wallace MC et al. Association between ABCG2 rs2231142 and poor response to allopurinol: replication and meta-analysis. Rheumatology (Oxford) 2018;57:656-60. PMID: 29342288.</td>
<td>3</td>
<td>299 gout patients, treated with allopurinol, could be classified as good responders (serum uric acid <0.36 mmol/L on allopurinol ≤300 mg/day) or poor responders (serum uric acid ≥0.36 mmol/L despite allopurinol >300 mg/day). Of these patients, only 297 could be genotyped for Q141K. In this study, the investigators were encouraged but not required to increase allopurinol dose to achieve serum uric acid <0.36 mmol/L, with 61.9% of the patients included in this analysis having had at least one increase in allopurinol dose.
In addition, patients from the study of Roberts 2017 were analysed after extension of the number of patients that could be classified as good or poor responders to 252 for Q141K and 254 for rs10011796 after dose escalation in more patients in this cohort.
Patients with plasma oxypurinol <20 µmol/L (new group) or plasma oxypurinol <10 µmol/L (Roberts 2017 group) were considered to be nonadherent with allopurinol and excluded from the analyses. In the Roberts 2017 study, adherence was determined by observing a reduc-</td>
<td>Author’s conclusion:
”This study has confirmed the significant association of ABCG2 rs2231142 with poor response to allopurinol.”</td>
</tr>
</table>

ref. 6, continuation

tion in serum uric acid with increasing allopurinol dose for patients without oxypurinol data.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded.
Association of ABCG2 SNPs Q141K and rs10011796 with poor response was tested with logistic regression with adjustments made for age, sex, BMI, ethnicity and eGFR. The power to detect the association of Q141K with allopurinol response described by Roberts 2017 was 100% in the new cohort (n = 297). The power to detect the association of rs10011796 effect size described by Wen 2015 was 63% in both cohorts combined. Results of both cohorts were combined by meta-analysis. Due to the absence of significant heterogeneity between the two studies, a fixed-effects model was used for the meta-analyses.

Genotyping:

New group:		Extended Roberts 2017 group:	
Q141K:	rs10011796C>T:	Q141K:	rs10011796C>T:
- 183x QQ	- 61x CC	- 137x QQ	- 39x CC
- 99x QK	- 142x CT	- 89x QK	- 125x CT
- 15x KK	- 96x TT	- 26x KK	- 90x TT

Results:

% of patients with poor response for 141KK versus 141QK versus 141QQ or for rs10011796TT versus rs10011796CT versus rs10011796CC:

		141KK or rs10011796 TT	141QK or rs10011796 CT	value for 141QQ or rs10011796CC
141KK: A 141QK: A	Q141K	new group	x 2.0	x 1.7	37%
			OR_{adj} = 2.56 (95% CI: 1.62-4.14) (S).		
			OR_{adj} was similar after additional adjustment for rs10011796C>T (S).		
		Roberts 2017 group	x 2.1	x 1.6	39%
			OR_{adj} = 2.43 (95% CI: 1.53-3.95) (S).		
			OR_{adj} was similar after additional adjustment for rs10011796C>T (S).		
		meta-analysis	OR = 2.42 (95% CI: 1.71-3.45) (S).		
			OR was similar in a pooled analysis of 505 patients from both cohorts with adjustment for a genetic measure of ethnicity (the first four principal components) instead of adjustment for ethnicity (S).		
rs10011796TT: AA rs10011796 CT: AA	rs10011796C>T	new group	x 1.8	x 1.4	31%
			OR_{adj} = 1.55 (95% CI: 1.08-2.23) (S).		
			OR_{adj} lost significance after additional adjustment for Q141K (NS).		
		Roberts 2017 group	NS		
		meta-analysis	NS		
			Results were also NS in a pooled analysis of 505 patients from both cohorts with adjustment for a genetic measure of ethnicity (the first four principal components) instead of adjustment for ethnicity.		

There was no interaction between Q141K and rs10011796C>T. Neither was there an interaction between each of the genotypes and BMI and between Q141K and sex. So, these parameters do

<table>
<tr><td></td><td></td><td>not influence each other's effect on allopurinol response.</td><td></td></tr>
<tr><td>ref. 7
Roberts RL et al.
ABCG2 loss-of-function polymorphism predicts poor response to allopurinol in patients with gout.
Pharmacogenomics J 2017;17:201-3.
PMID: 26810134.</td><td>4

141KK: A

141QK: A

rs1001 1796TT : AA

rs1001 1796 CT: AA</td><td>188 gout patients, treated with allopurinol, could be classified as good responders (serum uric acid <0.36 mmol/L on allopurinol ≤300 mg/day) or poor responders (serum uric acid ≥0.36 mmol/L despite allopurinol >300 mg/day). Of these patients, only 183 could be genotyped for rs10011796TT.
Patients with plasma oxypurinol <10 µmol/L (1.5 mg/dl) were considered to be nonadherent with allopurinol and excluded from the analysis. Where an oxypurinol concentration was not available, adherence was determined by observing a reduction in serum uric acid with increasing allopurinol dose.
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded, but one of the adjustment schemes included diuretic use.

Genotyping:
Q141K: - 107x QQ - 65x QK - 16x KK
rs10011796C>T: - 31x CC - 85x CT - 67x TT

Results:
% of patients with poor response for 141KK versus 141QK versus 141QQ or for rs10011796TT versus rs10011796CT versus rs10011796CC:
Q141K: 141KK x 2.8; 141QK x 2.0; value for 141QQ 24%
OR = 2.71 (95% CI: 1.70-4.48) (S).
Similar results were obtained after adjustment for:
- age, sex, BMI, and ethnicity: OR_{adj} = 2.91 (95% CI: 1.71-5.17) (S).
- age, sex, BMI, ethnicity, and eGFR: OR_{adj} = 2.90 (95% CI: 1.69-5.17) (S).
- age, sex, BMI, ethnicity, and diuretic use: OR_{adj} = 3.06 (95% CI: 1.77-5.53) (S).
- age, sex, BMI, ethnicity, and pre-treatment serum uric acid concentration: OR_{adj} = 3.43 (95% CI: 1.83-6.83) (S).
- age, sex, BMI, ethnicity, and frequency of gout flares: OR_{adj} = 2.78 (95% CI: 1.57-5.09) (S).
rs10011796C>T: NS for rs10011796TT versus rs10011796CT versus rs10011796CC</td><td>Author's conclusion:
"ABCG2 rs2231142 predicts poor response to allopurinol, as defined by serum urate ≥6 $mgdl^{-1}$ despite allopurinol >300 mgd^{-1}."</td></tr>
<tr><td>ref. 8
Petru L et al.
Genetic background of uric acid metabolism in a patient with severe chronic tophaceous gout.
Clin Chim Acta 2016;460:46-9.
PMID: 27288985.</td><td>2

141QK: D</td><td>A 41-year old White male with partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency that results in uric acid overproduction, had developed severe chronic tophaceous gout, requiring repeated surgical intervention, and uric acid nephropathy despite treatment with allopurinol in different doses since the age of 13 years. Allopurinol doses used in the last 11.5 years were 200, 300, 400, 600 and 900 mg/day. However, despite treatment with full doses of allopurinol, long-term serum uric acid levels were poorly controlled, with most measurements showing serum uric acid concentrations above 0.446 mmol/L (up to 0.77 mmol/L). Adherence to allopurinol in the patient was confirmed 11 years earlier (plasma oxypurinol concentration 40.0 µmol/L) and 5 years earlier (plasma oxypurinol concentration 70.2 µmol/L).
Other drugs included corticosteroids (regularly), nonsteroidal anti-inflammatory drugs, and colchicine (intermittently).
Sequencing of all exons and exon/intron boundaries of ABCG2 revealed heterozygosity for the 141K allele and the presence of five intronic variants.</td><td>Author's conclusion:
"ABCG2 rs2231142 predicts poor response to allopurinol, as defined by serum urate ≥6 $mgdl^{-1}$ despite allopurinol >300 mgd^{-1}."</td></tr>
</table>

<table>
<tr><td>ref. 8, continuation</td><td></td><td>Because of the inefficacy of allopurinol and signs of mild renal insufficiency, the urate-lowering therapy was changed to febuxostat with an improvement in serum uric acid concentrations.</td><td></td></tr>
<tr><td>ref. 9
Wen CC et al. Genome-wide association study identifies ABCG2 (BCRP) as an allopurinol transporter and a determinant of drug response. Clin Pharmacol Ther 2015;97:518-25.
PMID: 25676789.</td><td>4

rs10011796-carrier: A

rs3114020-carrier: AA

141KK: AA

141QK: AA

rs2725271-carrier: AA

rs11732936-carrier: AA

rs74904971-carrier: AA

rs4148155-carrier: AA</td><td>A genome-wide association study for allopurinol response was performed for a total of 2027 patients, including 1607 non-Hispanic Whites, 238 Asians, 84 African Americans, and 85 Hispanics. For 1492 of the non-Hispanic Whites, a separate genome-wide association study was performed. The median allopurinol dose was 201 mg/day.
The outcome assessed in this study was the decrease in serum uric acid (treated - untreated) for the first allopurinol prescription for which both untreated and treated values were available. Serum uric acid values were adjusted for BMI, age, gender, and concomitant medications (diuretics and urate-lowering drugs) by linear regression. The difference was adjusted for cumulative allopurinol dose using a spline regression. For all ethnicities, a meta-analysis of separate genome wide association assays for each ethnicity was performed using a random effects model. Results were adjusted for baseline serum uric acid, age, current dose, BMI, gender, concomitant medications (diuretics and urate-lowering drugs), and the top population structure principal component (a genetic measure of ethnicity).
Co-medication with influence on ABCG2 or serum uric acid concentrations was not excluded, but uric acid concentrations were adjusted for diuretics and urate-lowering drugs.

Results:
<table>
<tr><td colspan="3">Associations with allopurinol response:</td></tr>
<tr><td rowspan="4">genome wide association study of allopurinol response (decrease in serum uric acid concentration)</td><td rowspan="2">non-Hispanic Whites</td><td>The strongest association with response to allopurinol was found for ABCG2 (rs10011796) (S).
Weaker associations, not reaching genome-wide significance, were found for two other ABCG2 SNPs (rs3114020 and Q141K) (NS).
The 141K allele was associated with a poorer response. When compared to the residuals after adjusting for nongenetic factors, this variant could account for 1.1% of the unexplained variance in non-Hispanic Whites.</td></tr>
<tr><td>No associations were found for SNPs of other genes previously reported to be associated with gout and/or baseline uric acid concentrations.</td></tr>
<tr><td rowspan="2">all ethnicities</td><td>Only associations not reaching genome-wide significance were found for ABCG2 SNPs, the strongest five being rs2725271, rs11732936, Q141K, rs74904971, and rs4148155 (NS).</td></tr>
<tr><td>A very weak association was found for rs10011796 with the p-value 34,500 times higher than in the non-Hispanic Whites.</td></tr>
<tr><td colspan="3">The authors consider Q141K most likely to be the most promising ABCG2 gene variant, since it is a known functional gene variant and its significance strengthened in all ethnicities (p-value 5.4 times smaller than in non-Hispanic Whites).</td></tr>
</table>
Note: In this cohort, Q141K does not associate with baseline serum uric acid concentration (NS).</td><td>Author’s conclusion:
”This first GWAS of allopurinol response demonstrates that ABCG2 is a key determinant of response to the drug.”</td></tr>
</table>

Risk group	High pre-treatment serum uric acid concentrations, high BMI, young age, male sex, diuretic use, high eGFR

Comments:
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Date of literature search: 13 January 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	141QK	4 D	yes	yes	7 June 2021
	141KK	4 A	yes	yes	

Mechanism:
Allopurinol is rapidly converted in the body to the active metabolite oxypurinol, which is responsible for most of the uric acid lowering effect. Allopurinol and oxypurinol lower uric acid by diminishing the uric acid production. They inhibit the enzyme xanthine oxidase, that degrades hypoxanthine and xanthine into uric acid.
The ATP Binding Cassette Transporter, Subfamily G, Member 2 (ABCG2) is an efflux transporter playing an important role in excretion of uric acid into the kidneys and intestinal tract. In addition, oxypurinol has been reported to be a substrate of ABCG2. The mechanism by which ABCG2 Q141K alters allopurinol response is unclear. On the one hand is it likely, that a stronger inhibition of uric acid production and thus a higher allopurinol dose is required in patients with a diminished uric acid excretion, like 141K-carriers. On the other hand would diminished excretion of oxypurinol predict higher oxypurinol concentrations and thus a higher effectiveness of allopurinol in 141K-carriers. However, the latter mechanism does not seem to happen. For 141K-carriers, the plasma concentration of oxypurinol was found to be lower instead of higher, suggesting that the variant allele increases oxypurinol secretion.
ABCG2 is an uric acid efflux transporter and reports suggest an association between ABCG2 Q141K and hyperuricemia and gout, resulting in a higher frequency of the 141K allele in hyperuricemic patients, so in patients with an indication for allopurinol.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	

OR • At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	1+
Corresponding Clinical Implication Score:		Potentially beneficial