CYP3A5: tacrolimus 2762/2763

AUC = area under the concentration-time curve, C_0 = trough concentration, CI = confidence interval, Cl_{or} = oral clearance, CYP3A5 non-expresser = no CYP3A5 enzyme activity (e.g. *3/*3 (the most common genotype)), eGFR = estimated glomerular filtration rate, heterozygous CYP3A5 expresser = moderate CYP3A5 enzyme activity (e.g. *1/*3), homozygous CYP3A5 expresser = high CYP3A5 enzyme activity (*1/*1), HR = hazard ratio, HR_{corr} = corrected hazard ratio, NS = non-significant, OR = odds ratio, OR_{corr} = corrected odds ratio, RR = relative risk, S = significant, $t_{1/2}$ = half-life, TDM = therapeutic drug monitoring.

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:
CYP3A5 converts tacrolimus to inactive metabolites. The required dose of tacrolimus is therefore higher in heterozygous and homozygous CYP3A5 expressers than in non-expressers (Teng 2024, Lenain 2021, Prasad 2019, Fernando 2019, Liu 2017, Yaowakulpatana 2016, Pulk 2015, Wang 2015, Buendia 2014, Uesugi 2014, Satoh 2008, Fukudo 2008, Hesselink 2008, Kuypers 2007, Renders 2007, Mourad 2006, Cheung 2006, Uesugi 2006, Zhang 2005, Tada 2005, Macphee 2005, and Hesselink 2003).
As stringent therapeutic drug monitoring takes place, CYP3A5 expression only results in a concentration of tacrolimus that is too low during the first days of treatment (Shuker 2016, Thervet 2010, Hesselink 2008, Kuypers 2007, Roy 2006). There is insufficient evidence for a clinical effect of the low tacrolimus concentration in CYP3A5 expressers during these first few days (see below). As the aim is to achieve the target range of tacrolimus concentration as soon as possible, the decision was nevertheless taken to provide a recommendation to undertake action.
An overview of the clinical and kinetic effects per genotype 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. A substantiation of the (dose) recommendation is provided below.
Justification of recommendation
A study found no increase in graft failure for 289 heterozygous and 60 homozygous CYP3A5 expressers (Seibert 2018) and a meta-analysis of 2 studies with a total of 166 patients found no increase in graft failure within 1 year (Tang 2011).
A study found for 17 heterozygous + 3 homozygous CYP3A5 expressers a reduced incidence of renal function abnormalities in liver transplant patients (Fukudo 2008). Another study found a non-significantly increased incidence of tacrolimus-related nephrotoxicity in kidney transplant patients for 15 heterozygous expressers (Kuypers 2007). A meta-analysis found an increase in the risk of chronic nephrotoxicity in 4 studies involving a total of 664 patients (OR = 2.42), but not in 5 studies involving a total of 867 patients (Rojas 2015).
A study in kidney patients found an increase in the incidence of acute rejections for both homozygous and heterozygous expressers in the Black group (HR_{corr} = 39 and 6.3, respectively) (246 patients, among whom 54 homozygous and 126 heterozygous expressers), but not in the much larger White group (1226 patients, among whom 6 homozygous and 163 heterozygous expressers) (Seibert 2018). The number of acute rejections in the Black group in this study was only 14.
Another study found no effect on the incidence of acute rejection episodes in kidney transplant patients, but did find a decrease of the average time until the first rejection episode for a total of 56 heterozygous + homozygous expressers (Macphee 2005). Of four meta-analyses of kidney transplant studies, the largest found an increase in rejection episodes in the period 30-60 months after transplantation (OR = 1.68) (3 studies with a total of 513 patients), but not in three earlier periods and in all periods (25 studies with a total of 3181 patients), and in addition in Asians (OR = 1.62) (10 studies with a total of 1298 patients), but not in Europeans (13 studies with a total of 1579 patients) and in all ethnicities (25 studies with a total of 3181 patients) (Khan 2020). The one but largest meta-analysis found an increase in the risk of acute rejection (OR = 1.32) (21 studies with a total of 2185 patients), but this increase was only present in studies in which the diagnosis was based on clinical criteria and not in studies in which the diagnosis was based on biopsies (Rojas 2015). The one but smallest meta-analysis found no increase in the risk (10 studies with a total of 1246 patients) (Terrazzino 2012) and the smallest meta-analysis found an increase only

during the first month (2 studies with a total of 209 patients), but not over longer periods or over all periods (8 studies with a total of 772 patients) (Tang 2011). Therefore, there are some indications supporting an increased risk of acute rejection. However, as TDM for tacrolimus is not performed in the same way in all countries, there is no evidence that this also applies to the Netherlands, where the time to therapeutic tacrolimus trough concentration is less than ten days (Shuker 2016 and Hesselink 2008). Three studies in which tacrolimus starting dose was adjusted according to the genotype and a meta-analysis of five of these studies found no clinical effects of the genotype-guided dose adjustment (Yang 2021, Pallet 2016 and Thervet 2010, Shuker 2016, and Wang 2015), despite a higher incidence of the tacrolimus trough concentration within the therapeutic range in the meta-analysis (RR = 1.40) and a higher incidence of the tacrolimus trough concentration within the therapeutic range after the first 3 days of tacrolimus treatment in one of the studies (x 1.5-1.7 compared to the non-genotype-guided dose adjustment) (Yang 2021, and Pallet 2016 and Thervet 2010).
Some studies indicate a longer time to therapeutic tacrolimus trough concentration for heterozygous and homozygous CYP3A5 expressers (Roy 2006 and Macphee 2005). However, with use of TDM as performed in the Netherlands, the time to therapeutic tacrolimus trough concentration is less than ten days (Shuker 2016 and Hesselink 2008).
A study in 1114 kidney transplant patients (among whom 174 heterozygous and 34 homozygous expressers), restricting the tacrolimus dose after 1 year to 0.10 mg/kg per day, also if this resulted in tacrolimus trough concentrations below the target range of 5-7 ng/mL, showed a reduced decrease in eGFR over time from 1 year after transplantation without a decrease in patient-graft survival or death censored graft survival for CYP3A5 expressers (Lenain 2021). However, there is no confirmation from another study and one study is not enough evidence to recommend a deviation from the normal practice of titrating the dose based on the tacrolimus trough concentration.

<u>Dose recommendations</u>

For both heterozygous and homozygous expressers, there are studies listing the mean and median dose-corrected trough concentration or AUC compared to non-expressers. Therefore, two values were calculated from the literature: one based on the mean concentrations/AUCs and one based on the median concentrations/AUCs. For the median concentrations/AUCs, the weighted mean of the median concentrations from the individual studies was calculated.

Homozygous expresser	The dose adjustment calculated based on the studies using mean concentrations/AUCs (6 studies with a total of 91 homozygous expressers) is an increase up to 261% of the dose for non-expressers (208-418%, median 258%) (Teng 2024, Prasad 2019, Liu 2017, Renders 2007, Cheung 2006, and Zhang 2005). The dose adjustment calculated based on the studies using median concentrations/AUCs (4 studies with a total of 113 homozygous expressers) is an increase up to 252% of the dose for non-expressers (230-370%, median 265%) (Fernando 2019, Yaowakulpatana 2016, Pulk 2015, and Thervet 2010). As a precaution due to the toxicity of tacrolimus, the lowest value was maintained (252%) and this was rounded down to a percentage that can be used easily in practice, namely 250%. This corresponds well with the median dose-corrected tacrolimus trough concentration on day 3 being a factor 2.33 smaller in 9 homozygous expressers than in non-expressers in a Dutch study (Shuker 2016). Thervet 2010 found that the standard dose of 0.2 mg/kg per day in non-expressers resulted in high initial concentrations (median 16.6 ng/ml on day 3) and that lowering the dose to 0.15 mg/kg improved the percentage of patients with a tacrolimus trough concentration in the range 10-15 ng/ml on day 3. However, in a similar sized Dutch study, Shuker 2016 found that the standard dose of 0.2 mg/kg per day in non-expressers resulted in therapeutic initial concentrations (median 14.5 ng/ml on day 3) and that lowering the dose to 0.15 mg/kg did not improve the percentage of patients with a tacrolimus trough concentration in the range 10-15 ng/ml on day 3. In addition, both author groups mention that an initial target concentration of 10-15 ng/ml is high according to current standards (Pallet 2016 and Shuker 2016). For this reason, the median tacrolimus trough concentration on day 3 in 5 Dutch homozygous expressers on a starting dose of 0.3 mg/kg per day (9.4 ng/ml) is added to the recommendation to give health care professionals an impression of the effect of this dose in homozygous expressers.
Heterozygous expresser	The dose adjustment calculated based on the studies using mean concentrations/AUCs (7 studies with a total of 418 heterozygous expressers) is an increase up to 166% of the dose for non-expressers (129-246%, median 175%) (Teng 2024, Prasad 2019, Liu 2017, Kuypers 2007, Renders 2007, Cheung 2006, and Zhang 2005). The dose adjustment calculated based on the studies using median concentrations/AUCs (5 studies with a total of 792 heterozygous expressers) is an increase in the dose up to 160% of the dose for non-expressers (150-263%, median 155%) (Fernando 2019, Yaowakulpatana 2016, Pulk 2015, Thervet 2010, and Hesselink 2003). As a precaution due to the toxicity of tacrolimus, the lowest value was maintained (160%) and this was rounded down to a percentage that can be used easily in practice, namely 150%. This corresponds well with the median dose-corrected tacrolimus trough concentration

on day 3 being a factor 1.49 smaller in 56 heterozygous expressers than in non-expressers in a Dutch study (Shuker 2016).
Thervet 2010 found that the standard dose of 0.2 mg/kg per day in non-expressers resulted in high initial concentrations (median 16.6 ng/ml on day 3) and that lowering the dose to 0.15 mg/kg improved the percentage of patients with a tacrolimus trough concentration in the range 10-15 ng/ml on day 3. However, in a similar sized Dutch study, Shuker 2016 found that the standard dose of 0.2 mg/kg per day in non-expressers resulted in therapeutic initial concentrations (median 14.5 ng/ml on day 3) and that lowering the dose to 0.15 mg/kg did not improve the percentage of patients with a tacrolimus trough concentration in the range 10-15 ng/ml on day 3. In addition, both author groups mention that an initial target concentration of 10-15 ng/ml is high according to current standards (Pallet 2016 and Shuker 2016). For this reason, the median tacrolimus trough concentration on day 3 in 29 Dutch heterozygous expressers on a starting dose of 0.3 mg/kg per day (14.7 ng/ml) is added to the recommendation to give health care professionals an impression of the effect of this dose in heterozygous expressers.

In the case of liver transplants, the tacrolimus metabolism is determined by the genotypes of both the recipient and the donor (Wang 2015, Buendia 2014, Uesugi 2014, Fukudo 2008, and Uesugi 2006). There is insufficient evidence in the literature to support a dose recommendation if the genotypes of the recipient and the liver differ.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group decided not to give a genotyping recommendation for tacrolimus, because evidence of a clinical effect of CYP3A5 expresser phenotypes in standard clinical practice is lacking. Because of this, indications for a positive effect of determining CYP3A5 phenotype and adjusting therapy according to this phenotype are lacking.

The table below follows the KNMP nomenclature for CYP3A5 phenotypes (non-expresser, heterozygous expresser and homozygous expresser). The nomenclature for CYP3A5 phenotypes 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
Teng H et al. HDL-C and creatinine levels at 1 month are associated with patient 12-month survival rate after kidney transplantation. Pharmacogenet Genomics 2024;34:33-42. PMID: 37906625.</td>
<td>4

*1/*3: A
*1/*1: A</td>
<td>303 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and methylprednisolon. Tacrolimus trough concentrations were measured 7 days after transplantation. Relevant co-medication was excluded.

Genotyping:
- 162x *3/*3
- 135x *1/*3
- 12x *1/*1

Results:
<table>
<tr><td colspan="3">Dose-corrected tacrolimus trough concentration compared to *3/*3 (1.89 ng/ml per mg):</td></tr>
<tr><td>*1/*3</td><td>x 0.70</td><td rowspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
<tr><td>*1/*1</td><td>x 0.48</td></tr>
<tr><td colspan="3">Multivariable regression analysis confirmed *3/*3 to be an independent factor affecting the dose-corrected tacrolimus trough concentration (OR = 2.89 (95% CI: 1.69-4.95) (S)).</td></tr>
</table>
Note: Genotyping was for *3. This is the most important allele in this Chinese population.</td>
<td>Author’s conclusion:
”This study found that CYP3A5 *3/*3 is associated with high tacrolimus concentration/ dose ratio.”

Dose-corrected trough concentration compared to *3/*3 at day 7:
*1/*3: 70%
*1/*1: 48%</td>
</tr>
<tr>
<td>ref. 2
Lenain R et al. Impact of tacrolimus daily dose limitation in renal transplant recipients expressing CYP3A5: a retrospective study.</td>
<td>4</td>
<td>1114 kidney transplant patients were treated with tacrolimus-based therapy combined with mycophenolate mofetil (initially 2 g/day, thereafter tapered) and corticosteroids (500 mg at day 0, 250 mg at day 1, then 20 mg/day until day 7; steroids were stopped at day 8 for patients without immunological risk nor delayed graft function). The initial daily dose of tacrolimus was 0.15 mg/kg. Then, the dose was adjusted to reach C_0 between 10 and 15 ng/mL the first 3 months, 8 and 12 ng/mL within the first year, and later in a range from 5 to 7 ng/mL with tacrolimus daily dose that should not exceed 0.10 mg/kg per day regardless of CYP3A5 genotype. Follow-up was for a median of 6.3 years.</td>
<td>Author’s conclusion:
”Based on our experience, a strategy of tacrolimus capping is associated with a better glomerular filtration rate evolution in CYP3A5 *1/- recipients</td>
</tr>
</table>

<table>
<tr>
<td>J Pers Med 2021;11:1002. PMID: 34683143.

ref. 2, continuation</td>
<td>*1/*3+*1/*1: AA#</td>
<td>Patient-graft survival was defined as the time between transplantation and the first event among return to dialysis, pre-emptive re-transplantation, and death (all cause) with a functional graft. Death censored graft survival was defined as the time between transplantation and the first event among return to dialysis and pre-emptive re-transplantation (death was right censored). During follow-up 72 patients (6.5%) died with a functioning graft and 118 (10.8%) returned to dialysis.
Estimated glomerular filtration rate (eGFR) was defined according to the MDRD (Modification of Diet in Renal Disease) formula.
Biopsy proven acute rejection was defined according to Banff 2015 classification. During follow-up 171 patients (15.4%) had biopsy proven acute rejection.
Hazard ratios for (patient)-graft survival were determined using the Cox's proportional hazard model. Characteristics known to be associated with long-term survival were selected a priori to be included in the final model even if not significant (recipient and donor age, cold ischemia time, and previous transplantation).
Linear mixed model estimated by Restricted Maximum Likelihood was used to compare longitudinal changes in eGFR from 1 year post transplantation according to the CYP3A5 status.
The median time spent in dialysis was higher for *1/*3+*1/*1 than for *3/*3 (2.5 versus 2.1 years) (S). Patients treated with chronic drugs known to interfere with tacrolimus were excluded.

Genotyping:
- 906x *3/*3
- 174x *1/*3
- 34x *1/*1

Results:
<table>
<tr><td colspan="3">Results for *1/*3+*1/*1 compared to *3/*3:</td></tr>
<tr><td></td><td></td><td>value for *3/*3</td></tr>
<tr><td>patient-graft survival</td><td>trend for a lower HR_{corr} (p-value = 0.10) (NS)</td><td></td></tr>
<tr><td>death censored graft survival</td><td>NS</td><td></td></tr>
<tr><td>eGFR one year after transplantation</td><td>NS</td><td></td></tr>
<tr><td>eGFR mean decrease over time from one year after transplantation</td><td>- 2.57 mL/min/1.73m^2 per square root time unit (95% CI: -0.38 - -4.75) (S)</td><td></td></tr>
<tr><td>biopsy proven acute rejection</td><td>NS</td><td></td></tr>
<tr><td>daily dose at one year after transplantation</td><td>x 1.50 (S)</td><td>0.066 mg/kg</td></tr>
<tr><td rowspan="2">tacrolimus trough concentration at five years after transplantation</td><td>x 0.81 (S)</td><td rowspan="2">5.72 ng/mL</td></tr>
<tr><td>Due to the dose capping, for *1/*3+*1/*1, the mean tacrolimus trough concentration was lower dan the lower limit of the target range (5 ng/mL). This was the case from approximately 3 years after transplantation. At 5 years after transplantation, the tacrolimus trough concentration was below 5 ng/mL in 68% of *1/*3+*1/*1 and 30% of *3/*3.</td></tr>
<tr><td>dose-corrected</td><td>x 0.50 (S)</td><td>2.00</td></tr>
</table>
</td>
<td>without any significant increase of biopsy-proven acute rejection incidence. Our study raised some issues about specific therapeutic tacrolimus C_0 targets for CYP3A5*1/- patients and suggests to set up randomized control studies in this specific population."</td>
</tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td><table><tr><td>tacrolimus trough concentration</td><td></td><td>ng/mL per mg/kg</td></tr></table>
Note: Genotyping was for *3, and in patients without the *3/*3-genotype also for *6 and *7. These are the most important alleles in this French population.</td><td></td></tr>
<tr><td>ref. 3
Yang H et al. Clinical impact of the adaptation of initial tacrolimus dosing to the CYP3A5 genotype after kidney trans-plantation: systematic review and meta-analysis of randomized controlled trials. Clin Pharmacokinet 2021;60:877-85. PMID: 33751414.</td><td>3

Genotype-guided versus not genotype-guided dosing: A</td><td>Meta-analysis of 5 randomised controlled trials involving a total of 684 patients comparing CYP3A5 genotype-guided dosing with non-genotype-guided dosing in kidney transplant patients. One of the trials included heart and liver transplant patients next to kidney transplant patients.
The meta-analyses on the proportion of patients within the targeted concentration and on acute rejection included all 5 trials and a total of 650 and 684 patients, respectively. The meta-analyses on delayed graft function and on death censored graft survival included 3 trials and a total of 598 patients.
Four of the included trials had a low risk of bias on all 7 items of the Cochrane risk-of-bias tool. The fifth included trial had an uncertain risk of bias on the item allocation concealment (selection bias) and a low risk on the other 6 items.
Of the trials included in the meta-analysis, Shuker 2016 and Thervet 2010 were also included separately in this risk analysis.
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effects model in the absence of significant heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Potential publication bias was assessed by funnel plot only. This is insufficient.

Results:<table><tr><td colspan="2">Results for genotype-guided versus not genotype-guided dosing:</td></tr><tr><td>proportion of patients with tacrolimus exposure within the target range</td><td>RR = 1.40 (95% CI: 1.14-1.72) (S)</td></tr><tr><td>incidence of delayed graft function</td><td>NS</td></tr><tr><td>incidence of acute rejection</td><td>NS</td></tr><tr><td>incidence of death censored graft survival</td><td>NS</td></tr><tr><td colspan="2">There was no significant heterogeneity between the studies for all four comparisons.</td></tr><tr><td colspan="2">For all four comparisons, the funnel plot did not show obvious asymmetry. So, there were no indications for publication bias.</td></tr><tr><td colspan="2">Results did not change substantially after exclusion of individual studies one by one (investigated for all comparisons, except incidence of delayed graft function).</td></tr><tr><td colspan="2">Quality of evidence assessment according to the GRADE system showed the evidence to be of high quality for the proportion of patients with tacrolimus exposure within the target range and of moderate quality for the other three comparisons.</td></tr></table></td><td>Authors' conclusion:
"Although the genotype-guided group had a higher proportion of patients within the targeted concentration and less median time to achieve the therapeutic range, the clinical endpoints, including delayed graft function, acute rejection, graft survival censored for death, and adverse effects were similar in both groups. All in all, evidence suggested there was no utility in pharmacogenetics for tacrolimus based on the cytochrome P450 (CYP) 3A5 genotype."</td></tr>
<tr><td>ref. 4
Khan AR et al. CYP3A5 gene polymorphisms and their impact on dosage and trough concentration of tacrolimus among kidney trans-</td><td>3</td><td>Meta-analysis of 25 studies involving a total of 3181 kidney transplant patients. Of the 25 studies, 13 studies with a total of 1579 patients were performed in European populations and 10 studies with a total of 861 patients in Asian populations. Of the 25 studies, 4 studies with a total of 178 patients had a follow-up period of 1-2 weeks, 8 studies with a total of 1298 patients a follow-up period of 1-3 months, 8 studies with a total of 1330 patients a follow-up period of 12 months and 3 studies with a total of 513 patients a follow-up period of 36-60 months.
Of the 25 studies included in the meta-analysis, Hesselink 2003,</td><td>Authors' conclusion:
"No significant association was found with renal allograft rejection episodes between expressers and nonexpressers in Euro-</td></tr>
</table>

<table>
<tr>
<td>plant patients: a systematic review and meta-analysis. Pharmacogenomics J 2020;20:553-62. PMID: 31902947.

ref. 4, continuation</td>
<td>*1/*3+ *1/*1: E</td>
<td>Macphee 2005, Roy 2006, Kuypers 2007, and Hesselink 2008 were also included separately in this risk analysis.
Quality of the included studies was not assessed.
The protocol for this study was not preregistered. Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effects model in the absence of significant heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Potential publication bias was assessed by Egger's and Begg's tests, but results were only mentioned for the different follow-up categories.

Results:
<table>
<tr><td colspan="2">Graft rejection episodes for *1/*3+*1/*1 compared to *3/*3::</td></tr>
<tr><td>all ethnicities and follow-up periods</td><td>NS</td></tr>
<tr><td>1-2 weeks of follow-up</td><td>NS</td></tr>
<tr><td>1-3 months of follow-up</td><td>NS</td></tr>
<tr><td>12 months of follow-up</td><td>NS</td></tr>
<tr><td>36-60 months of follow-up</td><td>OR = 1.68 (95% CI: 1.01-2.79) (S)</td></tr>
<tr><td>European studies</td><td>NS</td></tr>
<tr><td>Asian studies</td><td>OR = 1.62 (95% CI: 1.16-2.24) (S)</td></tr>
<tr><td colspan="2">For all seven comparisons, there was no significant heterogeneity between the studies.</td></tr>
<tr><td colspan="2">For all follow-up categories, there was no publication bias.</td></tr>
</table>
</td>
<td>pean populations. Interestingly, Asian population (with expresser genotypes) and patients after 3 years post-transplantation (with expresser genotypes) have a higher risk of rejection."</td>
</tr>
<tr>
<td>ref. 5
Prasad N et al. Melding pharmacogenomic effect of MDR1 and CYP3A5 gene polymorphism on tacrolimus dosing in renal transplant recipients in Northern India. Kidney Int Rep 2019;5:28-38. PMID: 31922058.</td>
<td>4

*1/*3: A
*1/*1: A</td>
<td>248 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and steroid. Tacrolimus trough concentrations were measured a minimum of 3 times (3, 7, and 11 days after transplantation).
Relevant co-medication was excluded.

Genotyping:
- 123x *3/*3
- 94x *1/*3
- 31x *1/*1

Results:
<table>
<tr><td colspan="2">Dose-corrected tacrolimus trough concentration compared to *3/*3 (141.9 ng/ml per mg/kg):</td></tr>
<tr><td>*1/*3</td><td>x 0.77 (S)</td></tr>
<tr><td>*1/*1</td><td>x 0.39 (S)</td></tr>
</table>
Note: Genotyping was for *3. This is the most important allele in this northern Indian population.</td>
<td>Author's conclusion:
"Among CYP3A5 genotypic variants, the dose-adjusted tacrolimus level was significantly lower in CYP3A5 *1*1 (expressor) than that of CYP3A5*1*3 and CYP3A5*3*3."

Dose-corrected trough concentration compared to *3/*3 at day 3, 7, and 11:
*1/*3: 77%
*1/*1: 39%</td>
</tr>
<tr>
<td>ref. 6
Largeau B et al. Comparison of tacrolimus starting doses based on CYP3A5 phenotype or genotype in kidney transplant recipients. Prog Transplant 2019;29:300-8. PubMed PMID: 31514576.</td>
<td>3</td>
<td>Two groups of kidney transplant patients were treated with genotype-guided tacrolimus therapy combined with corticosteroids and mycophenolate mofetil or mycophenolic acid for 3 months. In the first group of 100 patients, the starting daily dose was 0.15 mg/kg for non-expressers and 0.30 mg/kg for expressers. In the second group of 107 patients, the starting daily dose was 0.10 mg/kg for non-expressers, 0.20 mg/kg for heterozygous expressers and 0.30 mg/kg for homozygous expressers. Daily doses were equally divided over 2 gifts. Tacrolimus dose was subsequently adjusted to achieve a trough concentration range of 8-12 ng/mL. Tacrolimus trough concentration was measured every 48 hours post-transplantation until patient discharge. Both mycophenolate mofetil/mycophenolic acid and corticosteroids were tapered. Induction therapy (basiliximab or antithymocyte globulin) was chosen depending on the immunological risk, especially HLA sensitization.
Delayed graft function was defined as the need for dialysis therapy within the first postoperative week. Patients with pre-emptive trans-</td>
<td>Author's conclusion:
"Our results confirm that selecting tacrolimus dosing regimen according to the expected phenotype is appropriate, but that lower than currently recommended doses may be preferable."</td>
</tr>
</table>

ref. 6, continuation

plantation (i.e. not needing dialysis at the time of transplantation) were excluded from delayed graft function analysis. The time required to reach the target trough concentration range was calculated based on the first tacrolimus trough concentration in the target range.
Relevant co-medication was not excluded.

Genotyping:

0.15 and 0.3 mg/kg group:	0.1, 0.2 and 0.3 mg/kg group:
- 77x *3/*3	- 90x *3/*3
- 20x *1/*3	- 14x *1/*3
- 3x *1/*1	- 3x *1/*1

Results:

Results compared to *3/*3 in the 0.15 and 0.3 mg/kg group:			
	*1/*1	*1/*3	value for *3/*3
recommended tacrolimus starting daily dose	x 2	x 2	0.15 mg/kg
median actual tacrolimus starting daily dose	x 1.4	x 0.86	0.14 mg/kg
median tacrolimus daily dose at day 10	x 2.8	x 2.0	0.10 mg/kg
median tacrolimus daily dose at discharge	x 2.6	x 1.6	0.10 mg/kg
% of patients with tacrolimus overexposure ($12 < C_0 < 20$ ng/ml)	x 0	x 0.39	63.6%
	S for *1/*1 versus *1/*3 versus *3/*3		
% of patients with tacrolimus toxic C_0 (> 20 ng/ml)	NS for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3		20.8%
% of patients with delayed graft function	NS for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3		23.2%
% of patients with acute rejection	NS for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3		7.8%
median time until target tacrolimus C_0	trend for a higher value for *1/*3 (p = 0.078) (NS)		3.0 days
median number of dose modifications until target C_0	NS for *1/*1 versus *1/*3 versus *3/*3		4.0

Results compared to *3/*3 in the 0.1, 0.2 and 0.3 mg/kg group:			
	*1/*1	*1/*3	value for *3/*3
recommended tacrolimus starting daily dose	x 3	x 2	0.10 mg/kg
median actual tacrolimus starting daily dose	x 3.1	x 2.2	0.09 mg/kg
median tacrolimus daily dose at day 10	x 2.0	x 2.2	0.10 mg/kg
median tacrolimus daily dose at discharge	x 1.8	x 2.0	0.10 mg/kg
% of patients with tacrolimus overexposure ($12 < C_0 < 20$ ng/ml)	NS for *1/*1 versus *1/*3 versus *3/*3		40.0%
% of patients with tacrolimus toxic C_0 (> 20 ng/ml)	x 5.0	x 0	13.3%

<table>
<tr>
<td>ref. 6, continuation</td>
<td>Genotype-guided therapy: 0.1, 0.2 and 0.3 mg/kg compared to 0.15 and 0.3 mg/kg: A</td>
<td>
<table>
<tr><td></td><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td><td></td></tr>
<tr><td>% of patients with delayed graft function</td><td colspan="2">NS for *1/*1 versus *1/*3 versus *3/*3</td><td>27.2%</td></tr>
<tr><td>% of patients with acute rejection</td><td colspan="2">NS for *1/*1 versus *1/*3 versus *3/*3</td><td>8.9%</td></tr>
<tr><td rowspan="2">median first tacrolimus C_0</td><td>x 2.4</td><td>x 0.75</td><td rowspan="2">7.9 ng/ml</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
<tr><td>median time until target tacrolimus C0</td><td colspan="2">NS for *1/*1 versus *1/*3 versus *3/*3</td><td>3.0 days</td></tr>
<tr><td>median number of dose modifications until target C_0</td><td colspan="2">NS for *1/*1 versus *1/*3 versus *3/*3</td><td>5.0</td></tr>
</table>
<table>
<tr><td colspan="3">Results for the 0.1, 0.2 and 0.3 mg/kg group compared to the 0.15 and 0.3 mg/kg group:</td></tr>
<tr><td></td><td></td><td>value for the 0.15 and 0.3 mg/kg group</td></tr>
<tr><td>% of patients with tacrolimus overexposure (12 < C_0 < 20 ng/ml)</td><td>x 0.71 (S)</td><td>54.0%</td></tr>
<tr><td>% of patients with tacrolimus toxic C_0 (> 20 ng/ml)</td><td>NS</td><td>20.0%</td></tr>
<tr><td>% of patients with tacrolimus overexposure or toxic C_0 (> 12 ng/ml)</td><td>x 0.69 (S)</td><td>74.0%</td></tr>
<tr><td>median time until target tacrolimus C0</td><td>NS</td><td></td></tr>
<tr><td>median number of dose modifications until target C_0</td><td>NS</td><td></td></tr>
</table>
Note: The authors state that results indicate that, in a real-life setting, a starting dose of 0.10 (non-expressers) and 0.20 (expressers) mg/kg per day could be more appropriate than the currently recommended ones of 0.15 and 0.30 mg/kg per day. They recognize that the number of CYP3A5*1/*1 patients was clearly too low to draw any definitive conclusions.

Note: The median recipient age was numerically higher for the *1/*1 patients (67 and 70 years) than for the *1/*3 and *3/*3 patients (ranging from 49 to 59 years). This was especially true in the 0.1, 0.2 and 0.3 mg/kg group where the minimum age for the *1/*1 patients was 64 years versus 39 years for the *1/*1 patients in the 0.15 and 0.3 mg/kg group and ranging from 18 to 41 years for the other genotypes.

Note: Genotyping was for *3. This is the most important allele in this French population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 7
Fernando ME et al.
Influence of CYP3A5 and ABCB1 polymorphism on tacrolimus drug dosing in South Indian renal allograft recipients.
Indian J Nephrol 2019;29:261-6.</td>
<td>4</td>
<td>101 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and corticosteroids (n = 99) or with azathioprine and corticosteroids (n = 2). Tacrolimus trough concentration was measured in the 6th month after transplantation. The target whole blood trough concentration was 8-10 ng/ml during the first 6 months.
Relevant co-medication was excluded.

Genotyping:
- 41x *3/*3
- 48x *1/*3
- 12x *1/*1

Results:</td>
<td>Author’s conclusion:
”Median concentration/dose ratio was significantly lower in homozygous and heterozygous expresser group when compared with nonexpresser group.”

Median dose-</td>
</tr>
</table>

<table>
<tr>
<td>PubMed PMID: 31423060.

ref. 7, continuation</td>
<td>*1/*3: A
*1/*1: A</td>
<td>
Median dose-corrected tacrolimus trough concentration compared to *3/*3 (181.3 ng/ml per mg/kg):
<table>
<tr><td>*1/*3</td><td>x 0.38</td><td rowspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
<tr><td>*1/*1</td><td>x 0.27</td></tr>
</table>
Note: Genotyping was for *3. This is the most important allele in this South Indian population.
</td>
<td>corrected trough concentration compared to *3/*3 in month 6:
*1/*3: 38%
*1/*1: 27%</td>
</tr>
<tr>
<td>ref. 8
Seibert SR et al. Tacrolimus trough and dose intra-patient variability and CYP3A5 genotype: effects on acute rejection and graft failure in European American and African American kidney transplant recipients.
Clin Transplant 2018;32: e13424.
PubMed PMID: 30318646.</td>
<td>3

hom. expr.: E
het. expr.: E</td>
<td>
1226 White and 246 Black kidney transplant patients were treated with tacrolimus-based therapy combined with mycophenolate mofetil and corticosteroids. The duration of steroid therapy differed between transplant centres. 26 patients initially received cyclosporine, but were subsequently switched to tacrolimus, and the initial calcineurin inhibitor was unknown in 21 recipients. Tacrolimus dose was adjusted to achieve a trough concentration range that differed between transplant centres, but was generally 8-12 ng/ml in months 0 to 3 and 6-10 ng/ml thereafter. Tacrolimus trough concentration was measured twice a week in week 1-8, and twice a month in month 3-6. Induction therapy (basiliximab, alemtuzumab or antithymocyte globulin) was chosen depending on the immunological risk.
Acute rejection was defined as biopsy proven or clinically treated T-cell or antibody mediated rejection occurring within the first 6 months post-transplant. All cause graft failure was defined as a composite of return to dialysis therapy, re-transplantation, or death with function.
The coefficient of variation was defined as the ratio of the standard deviation to the mean in percent and was calculated for each set of five consecutive tacrolimus trough concentrations and corresponding doses in each subject for 6 months post-transplant.
Relevant co-medication was not excluded, but results were controlled for corticosteroid use.
Variability in tacrolimus dose was associated with acute rejection in this study. For this reason, hazard ratios for acute rejection were controlled for variability in tacrolimus dose. Coefficients of variation were controlled for transplant centre and time post-transplant.

Genotyping:
White:
- 1057x non-expressers
- 163x heterozygous expressers
- 6x homozygous expressers
Black:
- 66x non-expressers
- 126x heterozygous expressers
- 54x homozygous expressers

Results:
<table>
<tr><td colspan="5">Results compared to non-expresser:</td></tr>
<tr><td></td><td>ethnicity</td><td>homozygous expresser</td><td>heterozygous expresser</td><td>value for non-expresser</td></tr>
<tr><td rowspan="3">acute rejection</td><td>White</td><td>NS</td><td>NS</td><td>7.1%</td></tr>
<tr><td>Black</td><td>HR_{corr} = 39 (95% CI: 4.2-400) (S)</td><td>HR_{corr} = 6.3 (95% CI: 2.0-20) (S)</td><td>3.3%</td></tr>
<tr><td colspan="3">The number of acute rejections in the Black group was only 14.</td><td></td></tr>
<tr><td rowspan="2">graft failure</td><td>White</td><td>NS</td><td>NS</td><td>12.7%</td></tr>
<tr><td>Black</td><td>NS</td><td>NS</td><td>19.7%</td></tr>
<tr><td rowspan="2">coefficient of variation of tacrolimus dose</td><td>White</td><td>- 5.14 (95% CI: 2.62-7.68) (S)</td><td>- 2.57 (95% CI: 1.31-3.84) (S)</td><td>17.01%</td></tr>
<tr><td>Black</td><td>NS</td><td>NS</td><td>12.19%</td></tr>
<tr><td rowspan="2">coefficient of variation of tacrolimus trough concentration</td><td>White</td><td>+ 3.64 (95% CI: 1.14 - 6.12) (S)</td><td>+ 1.82 (95% CI: 0.57 - 3.06) (S)</td><td>24.94%</td></tr>
<tr><td>Black</td><td>trend for an increase (p =</td><td>trend for an increase (p =</td><td>28.40%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”In our African American cohort, each CYP3A5 loss-of-function allele was significantly associated with a reduction in the risk of acute rejection. …. CYP3A5 loss-of-function alleles were not associated with the risk for graft failure. Determining CYP3A5 loss-of-function status may be important for rejection risk assessment and individualized management of dosing in the early post-transplant course, but less important for long term outcomes.”</td>
</tr>
</table>

<table>
<tr><td>ref. 8, continuation</td><td></td><td>
<table>
<tr><td></td><td></td><td>0.07) (NS)</td><td>0.07) (NS)</td><td></td></tr>
</table>
Note: Genotyping was for *3, *6 and *7. These are the most important alleles in this population from the USA and Canada.
</td><td></td></tr>
<tr><td>ref. 9
Liu F et al. Long-term influence of CYP-3A5, CYP3A4, ABCB1, and NR1I2 polymorphisms on tacrolimus concentration in Chinese renal transplant recipients. Genet Test Mol Biomarkers 2017;21:663-73. PubMed PMID: 28945481.</td><td>4

*1/*1: A
*1/*3: A</td><td>223 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and corticosteroids. At day 7, dose-corrected tacrolimus trough concentration was available for 92% of patients (88% of *3/*3, 97% of *1/*3 and all *1/*1).
Co-medication with CYP3A inducers or inhibitors was excluded.

Genotyping:
- 112x *3/*3
- 88x *1/*3
- 23x *1/*1

Results:
<table>
<tr><td colspan="4">Dose-, but not bodyweight-corrected tacrolimus trough concentration compared to *3/*3:</td></tr>
<tr><td>time post-transplantation</td><td>*1/*1</td><td>*1/*3</td><td>value for *3/*3</td></tr>
<tr><td rowspan="2">7 days</td><td>x 0.39</td><td>x 0.49</td><td rowspan="2">2.26 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">15 days</td><td>x 0.45</td><td>x 0.55</td><td rowspan="2">2.32 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">1 month</td><td>x 0.46</td><td>x 0.57</td><td rowspan="2">2.41 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">3 months</td><td>x 0.51</td><td>x 0.60</td><td rowspan="2">2.61 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">6 months</td><td>x 0.51</td><td>x 0.60</td><td rowspan="2">2.74 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">1 year</td><td>x 0.54</td><td>x 0.56</td><td rowspan="2">2.73 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">2 years</td><td>x 0.47</td><td>x 0.56</td><td rowspan="2">3.10 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">3 years</td><td>x 0.52</td><td>x 0.56</td><td rowspan="2">2.88 ng/ml per mg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td rowspan="2">5 years</td><td>x 0.64</td><td>x 0.77</td><td rowspan="2">2.46 ng/ml per mg</td></tr>
<tr><td colspan="2">NS for *1/*1 versus *1/*3 versus *3/*3, and for (*1/*3+*1/*1) versus *3/*3</td></tr>
<tr><td colspan="4">Multivariable linear regression showed CYP3A5 genotype to be an independent predictor of dose-corrected tacrolimus trough concentration at 7 days, 3 months and 2 years after transplantation, explaining 3.0-5.4% of variability.</td></tr>
<tr><td colspan="4">Time post-transplantation affected the dose-corrected tacrolimus trough concentration within CYP3A5 genotypes (S). Dose-corrected tacrolimus trough concentration increased over time in *3/*3 (S).</td></tr>
</table>
Note: Genotyping was for *3. This is the most important allele in this Chinese population.</td><td>Author’s conclusion:
”Genotyping of the CYP3A4 and CYP3A5 genes should be considered with respect to determining tacrolimus dose regimens during the post-transplantation period.”

Dose-, but not bodyweight-corrected trough concentration at day 7 compared to *3/*3:
*1/*3: 49%
*1/*1: 39%</td></tr>
<tr><td>ref. 10
Pallet N et al. Long-term clinical impact of</td><td>4</td><td>Long-term clinical outcomes (more than 5 years after transplantation) were analysed for the patients in Thervet 2010. Long-term data were available for 212 patients (90% of the original group), 104 in the control group and 108 in the genotype-guided group.</td><td>Author’s conclusion:
”We conclude that optimization</td></tr>
</table>

adaptation of initial tacrolimus dosing to CYP3A5 genotype. Am J Transplant 2016;16:2670-5. PubMed PMID: 26990694. **ref. 10, continuation**	Genotype-guided versus not-genotype-guided therapy: A	Genotyping: control group: - 83x *3/*3 - 15x *1/*3 - 6x *1/*1 genotype-guided group: - 82x *3/*3 - 22x *1/*3 - 4x *1/*1 Results: Results for the genotype-guided group compared to the control group:	of initial tacrolimus dose using pharmacogenetic testing does not improve clinical outcomes."

		value for the control group
graft survival	NS	73.0% after 100 months
graft survival in surviving patients	NS	78.6% after 100 months
biopsy proven acute rejection	NS	25.7% over 100 months
death	NS	6%
cancer	NS	20%
infection	NS	55%
cardiovascular events	NS	17%
de novo donor-specific antibodies	NS	15%
Last follow-up visit:		
time after transplantation	NS	80 months
weight	NS	84 kg
systolic blood pressure	NS	136 mmHg
diastolic blood pressure	NS	79 mmHg
dose-corrected tacrolimus trough concentration	NS	1.5 ng/ml per mg
serum creatinine	NS	172 µmol/L
haemoglobin A1c	trend for an increase (p = 0.06) (NS)	5.7%
proteinuria	NS	0.7 g/L
tacrolimus trough concentration within the target range (10-15 ng/ml) after the first 3 days of tacrolimus treatment	x 1.68 (S)	25%

Note: The authors indicate that the patient group and transplantation protocol in this study may not be representative of the usual kidney transplant patients and protocols. Patients included in the study were highly selected with no expanded criteria donors, and had a low immunological risk. Even if the immunosuppressive regimen was the standard (corticosteroids, mycophenolate mofetil, and tacrolimus), the target tacrolimus trough concentrations were higher than those currently recommended, albeit that the optimal trough concentration ranges for preventing rejection are not defined. Finally, most of the patients received induction with thymoglobulin and high mycophenolate dosages, despite a low immunological risk (to allow the delay of the introduction of tacrolimus), which may participate in the low rejection rate (<10%) and the very good results in terms of graft survival in the whole cohort (90% at 5 years, 80% at nearly 10 years).

Note: The authors indicate that, given the low occurrence rate of graft loss in this follow-up study, a larger population would have been required to detect a small effect (if any) of genotype-guided tacrolimus dosing on graft survival.

Note: Genotyping was for *3. This is the most important allele in this French population.

<table>
<tr>
<td>ref. 11
Shuker N et al. A randomized controlled trial comparing the efficacy of Cyp-3a5 genotype-based with body-weight-based tacrolimus dosing after living donor kidney transplantation. Am J Transplant 2016;16:2085-96.
PubMed PMID: 26714287.</td>
<td>4

Genotype-guided versus not-genotype-guided therapy:
all: A
*3/*3: A
*1/*3: A
*1/*1: AA</td>
<td>237 kidney transplant patients were treated with tacrolimus combined with corticosteroids and mycophenolate mofetil. 119 patients received an initial dose of 0.1 mg/kg every 12 hours. The other 118 patients received an initial dose that was modified according to the genotype: 0.075 mg/kg every 12 hours for *3/*3 and 0.15 mg/kg every 12 hours for *1/*3 and *1/*1. Tacrolimus trough concentration at day 3 was available for 104 patients in the genotype-guided group and 99 patients in the control group. 116 patients in the genotype-guided and 115 patients in the control group completed the 3-month follow-up period. Tacrolimus dose was adjusted to achieve a trough concentration range of 10-15 ng/ml in weeks 1 and 2, 8-12 ng/ml in weeks 3 and 4, and 5-10 ng/ml after week 4 post-transplantation. Tacrolimus trough concentration was routinely measured three times weekly during hospitalisation and at every outpatient clinic visit. All patients received basiliximab induction therapy and all received trimethoprim/sulfamethoxazole prophylaxis for at least 3 months. All patients being either seropositive for cytomegalovirus or receiving a kidney from a cytomegalovirus-positive donor received prophylaxis with valganciclovir for 6 months. 43% of patients was not on dialysis before transplantation.
Delayed graft function was defined as the need for dialysis therapy within the first postoperative week.
Immunosuppressive drug treatment within 28 days prior to transplantation (except glucocorticoids) and/or usage of any drugs known to interact with tacrolimus at the time of transplantation were excluded.
A study population of 196 patients (98 patients per treatment arm) was calculated to provide a statistical power of 80% to detect a difference between the two groups in the proportion of patients within the target tacrolimus trough concentration on day 3 after transplantation, assuming a 40% incidence in the standard dosing group and a 20% increase of this value in the genotype-guided dosing group.

Genotyping:
control group:
- 88x *3/*3
- 27x *1/*3
- 4x *1/*1
genotype-guided group:
- 84x *3/*3
- 29x *1/*3
- 5x *1/*1

Results:
<table>
<tr><td colspan="4">Results for the genotype-guided group compared to the control group:</td></tr>
<tr><td colspan="2"></td><td></td><td>value for the control group</td></tr>
<tr><td rowspan="3">% of patients with tacrolimus trough concentration within the target range (10-15 ng/ml) on day 3</td><td>all</td><td>NS</td><td>37.4%</td></tr>
<tr><td>*3/*3</td><td>NS</td><td>36.8%</td></tr>
<tr><td>*1/*3+ *1/*1</td><td>NS</td><td>39.1%</td></tr>
<tr><td rowspan="3">% of patients with subtherapeutic tacrolimus trough concentration (< 10 ng/ml) on day 3</td><td>all</td><td>trend for an increase (p = 0.10) (NS)</td><td>23.2%</td></tr>
<tr><td>*3/*3</td><td>x 2.42 (S)</td><td>15.8%</td></tr>
<tr><td>*1/*3+ *1/*1</td><td>NS</td><td>47.8%</td></tr>
<tr><td rowspan="3">% of patients with supratherapeutic tacrolimus trough concentration (> 15 ng/ml) on day 3</td><td>all</td><td>NS</td><td>39.4%</td></tr>
<tr><td>*3/*3</td><td>x 0.50 (S)</td><td>47.4%</td></tr>
<tr><td>*1/*3+ *1/*1</td><td>x 3.57 (S)</td><td>13.0%</td></tr>
<tr><td rowspan="4">median tacrolimus trough concentration on day 3</td><td>all</td><td>x 0.87 (S)</td><td>13.3 ng/ml</td></tr>
<tr><td>*3/*3</td><td>x 0.78 (S)</td><td>14.5 ng/ml</td></tr>
<tr><td>*1/*3</td><td>x 1.41 (S)</td><td>10.4 ng/ml</td></tr>
<tr><td>*1/*1</td><td>NS</td><td>6.8 ng/ml</td></tr>
<tr><td colspan="2">median of the average tacrolimus</td><td>x 0.98 (S)</td><td>13.1 ng/ml</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Pharmacogenetic adaptation of the tacrolimus starting dose does not increase the number of patients having therapeutic tacrolimus exposure early after transplantation and does not lead to improved clinical outcome in a low immunological risk population.”</td>
</tr>
</table>

ref. 11, continuation		trough concentration in week 1		
		median of the average tacrolimus trough concentration in week 2	x 0.93 (S)	12.5 ng/ml
		median time to target tacrolimus trough concentration	NS	6 days
		mean number of dose modifications to reach target tacrolimus trough concentration	NS	1.31
		% of patients with marked subtherapeutic tacrolimus trough concentration (< 5 ng/ml) in month 1	NS	10.3%
		% of patients with marked suprathe-rapeutic tacrolimus trough concentration (> 20 ng/ml) in month 1	NS	32.5%
		total number of adverse events	NS	728
		total number of serious adverse events	NS	148
		graft survival (including death with a functioning transplant)	NS	96.6%
		graft survival in surviving patients	NS	97.5%
		biopsy proven acute rejection	NS	10.1%
		presumed acute rejection	NS	4.2%
		delayed graft function	NS	4.2%
		median eGFR at 3 months after transplantation	NS	47 ml/min per 1.73 m^2
		each of the other adverse events, including post-transplant diabetes mellitus, acute tacrolimus-associated nephrotoxicity, and neurotoxicity	NS	
		Note: The authors indicate that it is unknown why the CYP3A5-based tacrolimus dosing approach of Thervet 2010 was beneficial in terms of early tacrolimus exposure, whereas this was not the case in their study. However, in contrast to their study, in which tacrolimus was started directly after transplantation, the initiation of tacrolimus treatment was delayed until day 7 after transplantation in the French trial. The authors postulate that, possibly, the between-patient variability in tacrolimus concentrations in the few first days after transplantation was higher than the variability after a week. Note: There was a marked numerical increase in dose-corrected tacrolimus trough concentration in *3/*3, but not in *1/*3+*1/*1 from day 30 to day 90. On day 3, the median dose-corrected tacrolimus trough concentration for *1/*3 and *1/*1 was 67% and 43% that for *3/*3, respectively. Note: Genotyping was for *3. This is the most important allele in this Dutch population.		
ref. 12 De Meyer M et al. Pharmacogenetic-based strategy using de novo tacrolimus once daily after kidney transplantation: prospective pilot study. Pharmacogenomics 2016;17:1019-	4	151 kidney transplant patients were treated with slow release tacrolimus (tacrolimus once daily, Advagraf) combined with corticosteroids and mycophenolate mofetil. Follow-up was 12 months. All patients received a single dose of tacrolimus once daily 0.10 mg/kg preceding transplantation. After transplantation, *3/*3 patients either received an initial daily dose of 0.2 mg/kg (n = 66) or an initial daily dose of 0.25 mg/kg (n = 62). *1/*3 patients received an initial daily dose of 0.3 mg/kg, and *1/*1 patients an initial daily dose of 0.35 mg/kg. Tacrolimus dose was adjusted (every three days in the first week) to achieve a trough concentration range of 10-15 ng/ml until day 21, 8-12 ng/ml from day 22 to day 90, and 5-8 ng/ml thereafter. Recipients of living donor kidneys (23% of patients) received basiliximab induction therapy. The rejection rate during the first year after transplantation was low in this study (6.6%). Delayed graft function was defined as the need for dialysis therapy	Author's conclusion: "On day 3, median C_{min} fell within the therapeutic range in all study groups. CYP3A5 expressors require significantly higher tacrolimus once daily throughout the follow-up period to achieve a comparable

<table>
<tr>
<td>27.
PubMed PMID: 27266721.

ref. 12, continuation</td>
<td>Genotype-guided therapy:
*1/*1: A
*1/*3: A</td>
<td>within the first postoperative week.
Drugs potentially interacting with tacrolimus were excluded.

Genotyping:
- 128x *3/*3
- 16x *1/*3
- 7x *1/*1

Results:
<table>
<tr><td colspan="6">Results compared to *3/*3 on registered initial daily tacrolimus dose (0.2 mg/kg):</td></tr>
<tr><td></td><td></td><td>*1/*1 on 0.35 mg/kg</td><td>*1/*3 on 0.3 mg/kg</td><td>*3/*3 on 0.25 mg/kg</td><td>value for *3/*3 on 0.2 mg/kg</td></tr>
<tr><td rowspan="3">% of patients with tacrolimus C_0 within the target range (10-15 ng/ml)</td><td>day 3</td><td>NS</td><td>NS</td><td>NS</td><td>about 38%</td></tr>
<tr><td>day 6</td><td>NS</td><td>NS</td><td>NS</td><td>about 48%</td></tr>
<tr><td colspan="5">Note: significance could not be determined for *1/*1 and *1/*3 due to the low number of patients. On day 3, the % of patients with tacrolimus C_0 within the target range was numerically markedly lower in *1/*3 (about 12%). The value for *1/*3 on day 6 and the values for *1/*1 were numerically somewhat higher than the value for *3/*3 on 0.2 mg/kg.</td></tr>
<tr><td rowspan="3">% of patients with subtherapeutic tacrolimus C_0 (< 10 ng/ml)</td><td>day 3</td><td>NS</td><td>NS</td><td>NS</td><td>about 13%</td></tr>
<tr><td>day 6</td><td>NS</td><td>NS</td><td>NS</td><td>about 25%</td></tr>
<tr><td colspan="5">Note: significance could not be determined for *1/*1 and *1/*3 due to the low number of patients. On day 3 and 6, the % of patients with subtherapeutic tacrolimus C_0 was numerically higher for *1/*1 and *1/*3 (about 29% to about 42%).</td></tr>
<tr><td rowspan="3">% of patients with supratherapeutic tacrolimus C_0 (> 15 ng/ml)</td><td>day 3</td><td>NS</td><td>NS</td><td>NS</td><td>about 46%</td></tr>
<tr><td>day 6</td><td>NS</td><td>NS</td><td>NS</td><td>about 25%</td></tr>
<tr><td colspan="5">Note: significance could not be determined for *1/*1 and *1/*3 due to the low number of patients. On day 3 and 6, the % of patients with subtherapeutic tacrolimus C_0 was numerically lower, especially for *1/*1 (about 25% and 0%, respectively).</td></tr>
<tr><td rowspan="6">median tacrolimus C_0</td><td>day 3</td><td colspan="3">NS for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg</td><td>14.1 ng/ml</td></tr>
<tr><td rowspan="3">day 6</td><td>x 0.72 (NS)</td><td>x 0.94 (NS)</td><td>x 1.09 (NS)</td><td rowspan="3">12.8 ng/ml</td></tr>
<tr><td colspan="3">S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg</td></tr>
<tr><td colspan="3">The value for *1/*1 was below the target range.</td></tr>
<tr><td rowspan="3">day 14</td><td>x 0.74 (S)</td><td>x 0.91 (NS)</td><td>x 0.98 (NS)</td><td rowspan="3">12.5 ng/ml</td></tr>
<tr><td colspan="3">S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg</td></tr>
<tr><td colspan="3">The value for *1/*1 was below the target range.</td></tr>
<tr><td>month 1</td><td>x 0.96</td><td>x 0.86</td><td>x 0.99</td><td>12.7</td></tr>
</table>
</td>
<td>C_{min}.”</td>
</tr>
</table>

ref. 12, continuation					(NS)	(S)	(NS)	ng/ml
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
					Only the value for *1/*3 was not above the target range.			
				month 3	NS for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			8.8 ng/ml
				month 6	x 1.14 (NS)	x 1.13 (NS)	x 1.11 (S)	7.0 ng/ml
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				month 12	NS for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			6.6 ng/ml
			median daily tacrolimus dose	day 1	x 1.75 (S)	x 1.50 (S)	x 1.25 (S)	0.20 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				day 3	x 1.84 (S)	x 1.58 (S)	x 1.21 (S)	0.19 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				day 6	x 2.11 (S)	x 1.78 (S)	x 1.22 (S)	0.18 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				day 14	x 2.17 (S)	x 1.83 (S)	x 1.11 (NS)	0.18 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				month 1	x 3.07 (S)	x 2.00 (S)	x 1.20 (NS)	0.15 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				month 3	x 3.67 (S)	x 2.56 (S)	x 1.11 (NS)	0.09 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				month 6	x 4.50 (S)	x 3.50 (S)	x 1.33 (NS)	0.06 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
				month 12	x 4.80 (S)	x 3.40 (S)	x 1.40 (NS)	0.05 mg/kg
					S for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			
			median estimated glomerular filtration rate	day 7, day 14, month 1, month 3 , month 6, and	NS for *1/*1 versus *1/*3 versus *3/*3 on 0.25 mg/kg versus *3/*3 on 0.2 mg/kg			39-56 ml/min

<table>
<tr><td>ref. 12, continuation</td><td></td><td>
<table>
<tr><td></td><td>month 12</td><td></td><td></td></tr>
</table>

Note: There was a marked numerical increase in dose-corrected tacrolimus trough concentration in *3/*3, but not in *1/*3 and *1/*1 from month 1. The timing seems to correspond with the end of methylprednisolone tapering (tapered to 4 mg/day by 6 weeks).
On day 3, the median dose-corrected tacrolimus trough concentration for *1/*3 and *1/*1 was 66% and 55% that for *3/*3, respectively.

Note: Genotyping was for *3. This is the most important allele in this Belgian population.</td><td></td></tr>
<tr><td>ref. 13
Yaowakulpatana K et al.
Impact of CYP3A5 polymorphism on trough concentrations and outcomes of tacrolimus minimization during the early period after kidney transplantation.
Eur J Clin Pharmacol 2016;72:277-83.
PubMed PMID: 26635230.</td><td>4

*1/*1: A
*1/*3: A</td><td>164 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and corticosteroids. A single tacrolimus dose of 0.1 mg/kg was given preoperatively, followed by a dose of 0.05 mg/kg twice daily after transplantation. Tacrolimus dose was adjusted to obtain a tacrolimus trough concentration of 4-8 ng/ml.
Co-medication interacting with tacrolimus was excluded (except corticosteroids).

Genotyping:
- 81x *3/*3
- 68x *1/*3
- 15x *1/*1

Results:
<table>
<tr><td colspan="4">Median daily dose-corrected tacrolimus trough concentration compared to *3/*3:</td></tr>
<tr><td>time post-transplantation</td><td>*1/*1</td><td>*1/*3</td><td>value for *3/*3</td></tr>
<tr><td rowspan="2">3 days</td><td>x 0.39</td><td>x 0.69</td><td rowspan="2">91 ng/ml per mg/kg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
<tr><td rowspan="2">7 days</td><td>x 0.48</td><td>x 0.65</td><td rowspan="2">91 ng/ml per mg/kg</td></tr>
<tr><td colspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
</table>

Note: Genotyping was for *3. This is the most important allele in this Thai population.</td><td>Author’s conclusion:
”CYP3A5 polymorphism significantly influenced the tacrolimus dose required to achieve the target concentration.”

Median dose-corrected trough concentration at day 3 and day 7 compared to *3/*3:
*1/*3: 67%
*1/*1: 44%</td></tr>
<tr><td>ref. 14
Pulk RA et al.
Multigene predictors of tacrolimus exposure in kidney transplant recipients.
Pharmacogenomics 2015;16:841-54.
PubMed PMID: 26067485.</td><td>3

*1/*3: A
*1/*1: A</td><td>2008 kidney transplant patients were treated with tacrolimus combined with mycophenolate mofetil and corticosteroids. Follow-up was for 6 months. The treatment regimen and patient groups differed between the 7 participating treatment centres. Target tacrolimus trough concentrations were generally 8-12 ng/ml in months 0-3 and 6-10 ng/ml in months 4-6. Two tacrolimus trough concentrations, if available, were obtained in each of weeks 1-8 and in each of months 3, 4, 5 and 6 post-transplant, for a maximum of 24 measurements per patient.
Relevant co-medication was not excluded, but multivariable linear mixed effects regression models adjusted for co-medication (antiviral, calcium channel blocker and steroid use at time of measurement).
The multivariable linear mixed effects regression models also adjusted for bodyweight.

Genotyping (estimated based on the allele frequency):
- 1285x *3/*3
- 643x *1/*3
- 80x *1/*1

Results:
<table>
<tr><td colspan="3">Median daily dose-, but not bodyweight-corrected tacrolimus trough concentration compared to *3/*3:</td></tr>
<tr><td>*1/*3</td><td>x 0.65</td><td rowspan="2">S for *1/*1 versus *1/*3 versus *3/*3</td></tr>
<tr><td>*1/*1</td><td>x 0.43</td></tr>
</table></td><td>Author’s conclusion:
”This study confirmed that CYP3A5*1 was associated with lower tacrolimus trough concentrations.”

Median dose-, but not bodyweight-corrected trough concentration in the first 6 months:
*1/*3: 65%
*1/*1: 43%</td></tr>
</table>

<table>
<tr><td>ref. 14, continuation</td><td></td><td>Note: The authors indicate that dose normalized trough concentrations initially started low, rose and then plateaued at day 9 post-transplant.

Note: Genotyping was for *3. This is the most important allele in this population from the USA.</td><td></td></tr>
<tr><td>ref. 15, liver
Wang L et al. Benefits of minimizing immunosuppressive dosage according to cytochrome P450 3A5 genotype in liver transplant patients: findings from a single-center study. Genet Mol Res 2015;14:3191-9. PubMed PMID: 25966085.</td><td>3

Genotype-guided therapy</td><td>Two subsequent groups of liver transplant patients were treated with tacrolimus. Follow-up was for 6 months in both groups. In the first group of 100 patients, the average tacrolimus starting dose was 4-6 mg/day. The dose was adjusted based on the physician’s judgment, clinical syndromes, trough concentration, renal function, and immune function. In the second group of 106 patients, for non-expressers receiving a liver from a non-expresser, the tacrolimus starting dose was 2 mg/day and this was increased to 3-4 mg/day. Great care was taken when increasing the tacrolimus dose in these patients. For patients being expressers and/or receiving a liver from an expresser, the starting dose was 4 mg/day, which was soon increased to 6 mg/day. Daily doses were divided over 2 gifts.
Liver toxicity was defined as transaminase levels exceeding the upper limit and/or bilirubin levels exceeding 50% of the upper limit of normal.
Renal toxicity was defined as serum creatinine >167 µM in patients with normal renal function before surgery or showing a >30% increase in patients with abnormal renal function before surgery (after the exclusion of other factors).
Neurotoxicity was defined as hand tremor, numb lips, and numbness in limbs.
Hypertension was defined as systolic pressure >140 mmHg or diastolic pressure >90 mmHg.
Hyperglycaemia was defined as blood glucose >7.0 mM for three consecutive days.
Concentration values influenced by fluconazole, amlodipine and nicardipine were excluded.
Significance of the differences in outcome between the genotype-guided group and non-genotype-guided group was not determined.

Genotyping:
Non-genotype-guided group:
- 24x *3/*3 + *3/*3-liver
- 21x *3/*3 + (*1/*3 or *1/*1)-liver
- 24x (*1/*3 or *1/*1) + *3/*3-liver
- 31x (*1/*3 or *1/*1) + (*1/*3 or *1/*1)-liver

Genotype-guided group:
- 25x *3/*3 + *3/*3-liver
- 26x *3/*3 + (*1/*3 or *1/*1)-liver
- 35x (*1/*3 or *1/*1) + *3/*3-liver
- 20x (*1/*3 or *1/*1) + (*1/*3 or *1/*1)-liver

Results:
<table>
<tr><td colspan="3">Results compared to the non-genotype-guided group:</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td>genotype-guided group</td><td>value for non-genotype-guided group</td></tr>
<tr><td rowspan="2">average tacrolimus dose over the 6-month period</td><td>NS</td><td rowspan="2">42.94 mg/day</td></tr>
<tr><td>The average tacrolimus dose in the patients being expressers and/or receiving a liver from an expresser was 1.45x the average dose in *3/*3 receiving a *3/*3-liver (45.76 versus 31.50 mg/day) (S).</td></tr>
</table></td><td>Author’s conclusion:
”Tailoring the tacrolimus dosage according to the CYP-3A5 genotype could reduce rejection and adverse effects.”</td></tr>
</table>

<table>
<tr>
<td>ref. 15, continuation</td>
<td>compared to non-genotype-guided therapy: AA

(*1/*3 or *1/*1) + (*1/*3 or *1/*1)-liver: A

(*1/*3 or *1/*1) + *3/*3-liver: A

*3/*3 + (*1/*3 or *1/*1)-liver: A</td>
<td>
<table>
<tr><td>% of patients with acute rejection</td><td>NS</td><td>19%</td></tr>
<tr><td>% of patients with hepatotoxicity</td><td>NS</td><td>9%</td></tr>
<tr><td>% of patients with renal toxicity</td><td>NS</td><td>25%</td></tr>
<tr><td>% of patients with neurotoxicity</td><td>NS</td><td>11%</td></tr>
<tr><td>% of patients with hypertension</td><td>NS</td><td>24%</td></tr>
<tr><td>% of patients with hyperglycemia</td><td>NS</td><td>24%</td></tr>
<tr><td>% of patients with Pneumocystis carinii infection</td><td>NS</td><td>4%</td></tr>
<tr><td colspan="3">The incidence of each of the adverse events was numerically lower in the genotype-guided group, but significance was not determined.</td></tr>
</table>

<table>
<tr><td colspan="5">Daily dose-corrected tacrolimus trough concentrations compared to *3/*3 + *3/*3-liver in the non-genotype-guided group:</td></tr>
<tr><td>time after transplantation</td><td>(*1/*3 or *1/*1) + (*1/*3 or *1/*1)-liver</td><td>(*1/*3 or *1/*1) + *3/*3-liver</td><td>*3/*3 + (*1/*3 or *1/*1)-liver</td><td>value for *3/*3 + *3/*3-liver (in ng/ml per mg/kg)</td></tr>
<tr><td>week 1</td><td>x 0.32 (S)</td><td>x 0.36 (S)</td><td>x 0.41 (S)</td><td>137.55</td></tr>
<tr><td>week 2</td><td>x 0.34 (S)</td><td>x 0.44 (S)</td><td>x 0.49 (S)</td><td>121.84</td></tr>
<tr><td>week 3</td><td>x 0.26 (S)</td><td>x 0.38 (S)</td><td>x 0.42 (S)</td><td>134.28</td></tr>
<tr><td>week 4</td><td>x 0.39 (S)</td><td>x 0.46 (S)</td><td>x 0.49 (S)</td><td>125.54</td></tr>
<tr><td>month 2</td><td>x 0.39 (S)</td><td>x 0.51 (S)</td><td>x 0.51 (S)</td><td>155.83</td></tr>
<tr><td>month 3</td><td>x 0.50 (S)</td><td>x 0.46 (S)</td><td>x 0.56 (S)</td><td>133.98</td></tr>
<tr><td>month 4</td><td>x 0.36 (S)</td><td>x 0.43 (S)</td><td>x 0.42 (S)</td><td>144.79</td></tr>
<tr><td>month 5</td><td>x 0.43 (S)</td><td>x 0.48 (S)</td><td>x 0.49 (S)</td><td>133.41</td></tr>
<tr><td>month 6</td><td>x 0.36 (S)</td><td>x 0.45 (S)</td><td>x 0.41 (S)</td><td>201.66</td></tr>
<tr><td colspan="5">The dose-corrected tacrolimus trough concentration in (*1/*3 or *1/*1) + (*1/*3 or *1/*1)-liver was not significantly lower than that in (*1/*3 or *1/*1) + *3/*3-liver and that in *3/*3 + (*1/*3 or *1/*1)-liver (NS).</td></tr>
<tr><td colspan="5">Similar results were obtained when the non-genotype-guided group and the genotype-guided group were analysed together.</td></tr>
</table>

Note: Genotyping was for *3. This is the most important allele in this Chinese population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 16
Rojas L et al. Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J 2015;15:38-48. PubMed PMID: 25201288.</td>
<td>3</td>
<td>Meta-analysis of 21 studies involving a total of 2,185 kidney transplant patients who were treated with oral tacrolimus twice daily. Of the studies included in the meta-analysis, Hesselink 2003, Macphee 2005, Roy 2006, Kuypers 2007 and Hesselink 2008 were also included separately in this risk analysis. All 21 studies were also included in the meta-analysis by Khan 2020. The follow-up in each of the studies varied from ≤ 1 month to > 12 months.
The quality of the included studies was assessed, but not with a known scale for quality assessment. Assessed were four selection criteria, two comparability criteria and two outcome criteria. Studies were considered to have a low risk of bias when all 8 criteria were met, a moderate risk of bias when 7 criteria were met and a high risk of bias when ≤ 6 criteria were met. Of the 21 studies, 2 had a low risk of bias, 5 a moderate risk of bias and the others a high risk of bias.
Meta-analyses were performed with a random-effects model. This indicates that the statistical method was chosen a priori. However, preregistration of the study protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias was assessed by funnel plot and Egger’s test.</td>
<td>Authors’ conclusion:
“CYP3A5 6986A>G polymorphism can affect tacrolimus pharmacokinetics and the incidence of acute rejection and chronic nephrotoxicity on kidney transplant recipients. Patients at high risk of developing tacrolimus-related complications could be detected even before</td>
</tr>
</table>

ref. 16, continuation	*1/*3 + *1/*1: E	(*1/*3 + *1/*1) compared to *3/*3: - increase in the risk of acute rejection (OR = 1.32; 95% CI: 1.02 - 1.71) (S). With a background risk of 16 acute rejections per 100 treated patients, this increased risk for CYP3A5 expressers would result in 4 additional acute rejections per 100 patients (95% CI: 0-9). The risk was elevated in studies in which the diagnosis was based on clinical criteria (OR = 5.04; 95% CI: 1.55 - 16.33), but not in studies in which the diagnosis was based on biopsies. There was no heterogeneity between the studies. - no difference in the risk of acute nephrotoxicity (3 studies involving a total of 363 patients) (NS). There was no heterogeneity between the studies. - no significant difference in the risk of chronic nephrotoxicity (5 studies involving a total of 867 patients) (NS). There was heterogeneity between the studies. Following exclusion of a study with unusually high incidence of chronic nephrotoxicity for *3/*3, the heterogeneity between the studies disappeared and there was an increase in the risk of chronic toxicity (OR = 2.42; 95% CI: 1.51 - 3.90) (4 studies involving a total of 664 patients) (S). For all three comparisons, there was no publication bias.	their kidney transplant."
ref. 17, liver Buendia JA et al. Effects of combinational CYP3A5 6986A>G polymorphism in graft liver and native intestine on the pharmacokinetics of tacrolimus in liver transplant patients: a meta-analysis. Ther Drug Monit 2014;36:442-7. PubMed PMID: 24378577.	3 *1/*3 + *1/*1: A	Meta-analysis of 8 studies involving a total of 694 adult liver transplant patients. Of the 8 studies in the meta-analysis, Fukudo 2008 was also included separately in this risk analysis. There was heterogeneity between the studies for most of the outcomes. Quality of the included studies was not assessed. Meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effects model in the absence of substantial heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Potential publication bias was not assessed. (*1/*3 + *1/*1) compared to *3/*3 (patient): - decrease in the dose-corrected trough concentration at 7 and 14 days and 1, 2, 3, 6 and 12 months after transplantation (S). After 7 days, the decrease in the dose-corrected trough concentration was 0.475 ng/mL per mg/kg per day (95% CI: 0.203 - 0.748 ng/mL per mg/kg per day). (*1/*3 + *1/*1) compared to *3/*3 (liver): - decrease in the dose-corrected trough concentration at 7 and 14 days and 1, 2, 3, 6 and 12 months after transplantation (S). After 7 days, the decrease in the dose-corrected trough concentration was 1.125 ng/mL per mg/kg per day (95% CI: 0.782 - 1.468 ng/mL per mg/kg per day). (*1/*3 + *1/*1) compared to *3/*3 (recipient/donor combinations) (2 studies involving a total of 109 patients): - *3/*3 recipient: no significant difference in the dose-corrected trough concentration 7 days after transplantation between a *3/*3 liver and a (*1/*3 + *1/*1) liver (NS). After 14 days, 1, 2, 3, 6 and 12 months, the dose-corrected trough concentration was lower for a (*1/*3 + *1/*1) liver than for a *3/*3 liver (S). - *3/*3 liver: lower dose-corrected trough concentration 7 days, 2, 3, 6 and 12 months after transplantation in a (*1/*3 + *1/*1) recipient than in a *3/*3 recipient (S). After 7 days, the decrease in the dose-corrected trough concentration was 0.866 ng/mL per mg/kg per day (95% CI: 0.186 - 1.546	Authors' conclusion: "In adult liver transplant patients, CYP3A5 expression in either the donor or recipient resulted in a need for a higher mean tacrolimus daily dose to achieve the target drug exposure. In the immediate post-transplant period, recipient expression of a CYP3A5*1 allele seemed to have the greatest influence on tacrolimus pharmacokinetics with donor expression of a CYP3A5*1 allele possibly becoming more important with increasing time after transplant."

		ng/mL per mg/kg per day).	
ref. 18, liver Uesugi M et al. Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-donor liver transplantation. Pharmacogenet Genomics 2014;24:356-66. PubMed PMID: 24911663.	4 *1/*3 + *1/*1: A	A total of 410 patients who received a liver transplant from a living donor were treated with tacrolimus-based therapy. Acute cellular rejection was only analysed in patients with a blood group that was compatible with that of the donor, who did not die within 14 days after transplantation and was also not analysed in 2 patients who underwent repeat transplantation. Patients whose blood group was not compatible with that of the donor received a different treatment regimen. High dose corticosteroids were used in the treatment of acute cellular rejection. As this treatment increases the CYP3A4 concentration in the intestines, the tacrolimus concentrations during the 4 days after high dose corticosteroids were not included in the analysis. Diagnosis of acute cellular rejection was based on an increase of trans-aminase and/or histology of liver biopsies taken between post-operative days 11 and 26. DNA for genotyping was obtained from intestinal or liver tissue and/or peripheral blood. *1/*1 versus *1/*3 versus *3/*3 (patient): - decrease in the dose-corrected trough concentration in weeks 1, 2, 3, 4 and 5 after transplantation (S). *1/*1 versus *1/*3 versus *3/*3 (liver): - decrease in the dose-corrected trough concentration in week 1 after transplantation (S). Only the difference between *1/*3 and *3/*3 was significant in weeks 2, 3 and 5. There were no significant differences in week 4. (*1/*3 + *1/*1) compared to *3/*3 (recipient/donor combinations): - *3/*3 recipient: - no significant difference in the dose-corrected trough concentration in weeks 1 through 5 after transplantation between a *3/*3 liver and a (*1/*3 + *1/*1) liver (NS). - increase in the frequency of acute cellular rejection from post-opera-tive day 14 to 23 for a (*1/*3 + *1/*1) liver compared to a *3/*3 liver (S) - (*1/*3 + *1/*1) recipient: - no significant difference in the dose-corrected trough concentration in weeks 1 through 5 after transplantation between a *3/*3 liver and a (*1/*3 + *1/*1) liver (NS). - no significant increase in the frequency of acute cellular rejection from post-operative day 14 to 23 for a (*1/*3 + *1/*1) liver compared to a *3/*3 liver (S). However, a (*1/*3 + *1/*1) liver was a risk factor for acute cellular rejection in the total group of recipients (see below). - *3/*3 liver: - lower dose-corrected trough concentration weeks 1 and 2 after transplantation in a (*1/*3 + *1/*1) recipient than in a *3/*3 recipient (S). - no difference in the frequency of acute cellular rejection from post-operative day 14 to 23 for a (*1/*3 + *1/*1) recipient compared to a *3/*3 recipient (NS). - (*1/*3 + *1/*1) liver: - lower dose-corrected trough concentration weeks 1 through 5 after transplantation in a (*1/*3 + *1/*1) recipient than in a *3/*3 recipient (S). - increase in the risk of acute cellular rejection from post-operative day 14 to 23 compared to a *3/*3 liver (RR = 2.629; 95% CI: 1.181 - 5.853) (S). - no difference in the frequency of acute cellular rejection from post-operative day 14 to 23 for a (*1/*3 + *1/*1) recipient compared to a *3/*3 recipient (NS). The authors indicated that the target value of the tacrolimus concentration may need to be revised for recipients of a (*1/*3 + *1/*1) liver.	Authors' conclusion: "The CYP3A5*3 genotype of the small intestine of recipients is more important as an indicator of the systemic exposure to tacrolimus for at least 5 weeks after transplantation than the CYP3A5*3 genotype of the graft liver, whereas there was a higher frequency of acute cellular rejection among patients receiving a liver with a CYP3A5*1 allele than among those receiving a liver with CYP3A5 *3/*3. …….. The CYP3A5*3 genotype of recipients may be important for estimation of the systemic pharmacokinetics of tacrolimus and it may be important to adjust the target level of tacrolimus after the initial post-transplantation period on the basis of the CYP3A5*3 genotype of the graft liver."

ref. 19 Terrazzino S et al. The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics 2012;22:642-5. PubMed PMID: 22786571.	3 *1/*3 + *1/*1: AA	Meta-analysis of 10 studies involving a total of 1,246 kidney transplant patients. Of the 10 studies included in the meta-analysis, Macphee 2005, Roy 2006 and Hesselink 2008 were also included separately in this risk analysis. All 10 studies were also included in the meta-analyses by Khan 2020 and Rojas 2015. However, Terrazzino only analysed the data about acute rejection confirmed by biopsy and did not include diagnoses based on clinical criteria. The quality of the included studies was not assessed. Meta-analyses were performed with a random-effects model. This indicates that the statistical method was chosen a priori. However, preregistration of the study protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised. Publication bias was assessed by funnel plot and Begg's and Egger's test. (*1/*3 + *1/*1) compared to *3/*3: - no difference in the risk of acute rejection (NS). There was heterogeneity between the studies, but no publication bias.	Authors' conclusion: "From the current evidence available, CYP3A5 6986A >G and ABCB1 3435C>T polymorphisms seem to have little or no effect on the acute rejection rates in renal transplant patients under immunosuppressive therapy with tacrolimus."
ref. 20 Tang HL et al. Lower tacrolimus daily dose requirements and acute rejection rates in the CYP3A5 non-expressors than expressors. Pharmacogenet Genomics 2011;21:713-20. PubMed PMID: 21886016.	3 *1/*3 + *1/*1: D	Meta-analysis of 8 studies involving a total of 772 kidney transplant patients. Of the 8 studies included in the meta-analysis, Macphee 2005, Roy 2006 and Hesselink 2008 were also included separately in this risk analysis. All 8 studies were also included in the meta-analyses by Khan 2020 and Rojas 2015 and 7 of the 8 were included in the meta-analysis by Terrazzino. Quality of the included studies was not assessed. Meta-analyses were performed with a random-effects model in case of substantial heterogeneity between the studies and with a fixed-effects model in the absence of substantial heterogeneity. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Potential publication bias was not assessed. (*1/*3 + *1/*1) compared to *3/*3: - increase in the risk of acute rejection during the first month (OR = 3.27; 95% CI: 1.57 - 6.81) (2 studies, 209 patients) (S), but not during the first 3 months, in the first 12 months or in total (NS). There was heterogeneity between the studies when considering the data over 12 months and over the total. - no difference in the risk of death within 1 year (two studies, 163 patients) (NS). - no difference in the risk of survival of the transplant for less than 1 year (two studies, 166 patients) (NS).	Authors' conclusion: "The acute organ rejection rate may be higher in CYP3A5 expressors than non-expressors over the first month after transplantation."
ref. 21 Thervet E et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther 2010;87:721-6. PubMed PMID: 20393454.	4	236 adult kidney transplant patients were treated with tacrolimus from day 7 after transplantation. 120 patients received an initial dose of 0.1 mg/kg twice daily. The other 116 patients received an initial dose that was modified according to the genotype: 0.075 mg/kg twice daily for *3/*3 and 0.15 mg/kg twice daily for *1/*3 and *1/*1. Patients were monitored for a period of 3 months. Patients whose blood group was not compatible with the transplant were excluded. The target range for the tacrolimus concentration was 10 - 15 ng/mL. All patients received induction therapy and the immunosuppressive co-medication during tacrolimus therapy (mycophenolate mofetil and corticosteroids) was similar for all patients. Medication with a known effect on CYP3A5 was excluded. Genotyping: Control group: - 6x *1/*1 Group with genotype-based dosing: - 4x *1/*1	Authors' conclusion: "Pharmacogenetic adaptation of the daily dose of tacrolimus is associated with improved achievement of the target C0. Whether this improvement will affect clinical outcomes requires further evaluation."

ref. 21, continuation	Genotype-guided versus not-genotype-guided therapy: *1/*1: A *1/*3: AA *3/*3: A	- 18x *1/*3 - 22x *1/*3 - 96x *3/*3 - 90x *3/*3 Genotype-based dosing versus control: - increase in the percentage of patients with a trough concentration within the target range after 3 days of tacrolimus by a factor 1.5 (from 29.1% to 43.2%) (S). - *1/*1: increase in the median trough concentration on day 3 from 5.6 to 14.0 ng/mL (S). As a result, the median trough concentration increased from being below the target range to being within the target range. - *1/*3: no significant increase in the median trough concentration on day 3 (from 10.1 to 12.3; both within the target range) (NS). - *3/*3: decrease in the median trough concentration on day 3 from 16.6 to 12.0 ng/mL (S). As a result, the median trough concentration decreased from being above the target range to being within the target range. - decrease in the time required to achieve a trough concentration within the target range from 7 to 6 days (S). - decrease in the number of dose adjustments in the group by 33% (from 420 to 281) (S). - no difference in delayed transplant function (incidence, number of dialysis sessions per patient and the number of patients with and the number of episodes of acute rejection) (NS). There was no correlation between acute rejection and genotype (NS). - no difference in transplant function (glomerular filtration speed on days 14 and 90), percentage of patients that died and survival of transplants (NS). - no difference in the occurrence of adverse events, also no difference in the occurrence or worsening of diabetes mellitus, or in the number of infections that occurred. *1/*1 versus *1/*3 versus *3/*3: - the median trough concentration after 3 days of tacrolimus 0.1 mg/kg twice daily was 5.6 versus 10.1 versus 16.6 ng/mL (significance not determined) NB1: In this article, *3/*3 patients had a median trough concentration above the target range of 10 - 15 ng/mL at a dose of 0.1 mg/kg twice daily. The initial dose recommended in the Informatorium for kidney transplant patients is 0.1 – 0.15 mg/kg twice daily. The Paediatric Formularium recommends a dose of 0.15 mg/kg twice daily. However, Dutch hospitals have indicated that the target value of the tacrolimus concentration in the first 2 or 4 weeks after kidney transplantation is 15 - 20 ng/mL. NB2: The authors cited 2 articles that demonstrated that the AUC for tacrolimus on day 2 is significantly lower for patients with acute rejection.	Median trough concentration of tacrolimus compared to *3/*3 after 3 days: *1/*3: 61% *1/*1: 34%
ref. 22 Satoh S et al. Lack of tacrolimus circadian pharmacokinetics and CYP-3A5 pharmacogenetics in the early and maintenance stages in Japanese renal transplant recipients.	3 *1/*3 + *1/*1: A	The oral clearance of tacrolimus was determined at 28 days and > 1 year after transplantation in 50 stable kidney transplant patients (3x *1/*1, 23x *1/*3, 24x *3/*3) on maintenance therapy with tacrolimus, mycophenolate mofetil and methylprednisolone. The average follow-up after transplantation was 26.7 months. Tacrolimus was started at a dose of 0.075 mg/kg twice daily, after which the dose was adjusted to achieve a trough concentration in the blood of 15 - 20 ng/mL during weeks 1 and 2, 10 - 15 ng/mL during weeks 3 and 4 and < 10 ng/mL thereafter (3 - 8 ng/mL after 1 year). (*1/*3 + *1/*1) compared to *3/*3: - decrease in $AUC_{0\text{-}12h}$[a] by 37% after 28 days and by 30% after > 1 year (S; resp. from 0.928 to 0.584 ng.h/mL per mg per kg and from 1.302 to 0.907 ng.h/mL per mg per kg). - increase in Cl_{or}[b] by 65% after 28 days (S; from 0.375 to 0.619 L/h	Authors' conclusion: "The CYP3A5 polymorphism may be associated with the time-dependent changes in the oral clearance of tacrolimus, suggesting that genotyping of this polymorphism is useful for determining

Br J Clin Pharmacol 2008;66:207-14. **ref. 22, continuation**		per kg) and by 25% after > 1 year (NS; from 0.319 to 0.399 L/h per kg). - increase in the percentage decrease of Cl_{or}[b] from the early post-transplantation phase to the maintenance phase by 97% (significance not determined; from 20% to 39%). Corticosteroids can induce CYP3A activity. The authors postulate that the decrease in the methylprednisolone dose per body weight over time (0.185 mg/kg after 28 days and 0.124 mg/kg after > 1 year; S) may be responsible for the decrease in Cl_{or}[b] of tacrolimus, particularly in the CYP3A5 expressers (*1/*3 + *1/*1).	the appropriate dose of tacrolimus in both the early and maintenance stages after renal transplantation."
ref. 23 Klauke B et al. No association between single nucleotide polymorphisms and the development of nephrotoxicity after orthotopic heart transplantation. J Heart Lung Transplant 2008;27:741-5.	3 *1/*3: AA *1/*1: AA	A case control study compared the data of 53 patients - of which 21 on tacrolimus and 32 on cyclosporin - who developed renal insufficiency after a heart transplant to the data of 53 controls who did not develop renal insufficiency. For all patients the immunosuppressive therapy consisted initially of cyclosporin and azathioprine. A total of 21 patients were switched from cyclosporin to tacrolimus at 10 - 12 days after the operation (initial dose 1 g twice daily, followed by dose adjustment to achieve a blood concentration of 6 - 10 mg/dL; mean dose at the time of the study was 4.19 mg/day). Co-medication consisted of (tem)sirolimus or everolimus (if necessary), statins, acetylsalicylic acid, bisphosphonates, calcium and vitamin D. *1/*1 versus *1/*3 versus *3/*3: - percentages of the genotypes in cases and controls are 0% versus 14% versus 86% and 8% versus 4% versus 88% respectively (NS, see below). - the CYP3A5 genotype was not associated with renal insufficiency.	Authors' conclusion: "Our data do not justify genotyping of the investigated single nucleotide polymorphisms (SNPs) to assess the development of renal dysfunction after cardiac transplantation."
ref. 24, liver Fukudo M et al. Impact of MDR1 and CYP3A5 on the oral clearance of tacrolimus and tacrolimus-related renal dysfunction in adult living-donor liver transplant patients. Pharmacogenet Genomics 2008;18:413-23.	3 *1/*3 + *1/*1: AA[#]	The oral clearance of tacrolimus during the first 50 post-operative days was determined using a population pharmacokinetic model in 60 liver transplant patients (3x *1/*1, 17x *1/*3, 40x *3/*3) on immunosuppressive therapy with tacrolimus and corticosteroids. Tacrolimus was started at an oral dose of 0.025 mg/kg twice daily, after which the dose was adjusted to achieve a trough concentration of 10 - 15 ng/mL during weeks 1 and 2, 10 ng/mL thereafter and 5 - 10 ng/mL after month 1. The dose during the first 50 days was 0.2 - 16.0 mg/day. Methylprednisolone was administered at a dose of 10 mg/kg i.v. during reperfusion of the transplant, after which the dose was gradually reduced. After 1 week the patients were switched to oral prednisolone, which was gradually reduced and - if possible - stopped after 3 - 6 months. Co-medication with strong inhibitors or inducers of CYP3A was excluded, but treatment of subclinical rejection episodes with intravenous high dose corticosteroids was permitted, as were low doses of fluconazole. (*1/*3 + *1/*1) compared to *3/*3: - increase in Cl_{or} in steady state (from day 14 onwards) by 47% (S). - increase in Bayesian estimates of Cl_{or} on days 7, 14, 21 and 28 (S), but non-significant differences on days 35, 42 and 49. - decrease in the dose-corrected trough concentration on day 7 by 38% and on day 14 by 29% (S). - no significant differences in dose-corrected trough concentrations after 1, 3, 6, 9 and 12 months. At these time points and on day 7, the CYP3A5 genotype of the transplant does have a significant effect on the dose-corrected trough concentration. - effectiveness of TDM: no significant differences in trough concentrations over the entire follow-up. - decrease in the cumulative incidence of renal function abnormalities within 1 year after transplantation by 63% (S; HR = 3.16 (95% CI 1.01 - 6.16); from 46 to 17%). The CYP3A5 genotype of the transplant has no significant effect on the incidence of renal function abnormalities. The authors postulate that CYP3A5 in the kidney protects against the development of renal function abnormalities, possibly through a	Authors' conclusion: "These findings suggest that the CYP3A5*1 genotype as well as the MDR1 mRNA level in enterocytes contributes to interindividual variation in the CL/F of tacrolimus in adult recipients early after living-donor liver transplantation. Furthermore, CYP3A5 in the kidney may play a protective role in the development of tacrolimus-related nephrotoxicity."

		reduction in the exposure of kidney cells to tacrolimus.	

ref. 25
Hesselink DA et al.
CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients.
Pharmacogenet Genomics 2008;18:339-48.
	4
	
	*1/*3 + *1/*1: A
		A prospective study involving 136 kidney transplant patients (5x *1/*1, 21x *1/*3, 110x *3/*3), who were being treated with tacrolimus, myco-phenolate mofetil and corticosteroids, determined the tacrolimus trough concentrations after 3 and 10 days and after 1, 3, 6 and 12 months. Induction therapy with either a monoclonal antibody targeted against the interleukin-2 receptor or anti-thymocyte globulin was permitted.
		
		(*1/*3 + *1/*1) compared to *3/*3:
		- decrease in the dose-corrected trough concentration at all time points. The decrease over the entire study period was 37% (after correction for age, gender and ethnicity) and 35% after addition of ABCB1 genotype to the model (S). The decrease remained significant after correction for corticosteroid dose and creatinine clearance.
		- significant versus non-significant decrease of the dose-corrected trough concentration between days 3 and 10.
		- non-significant change versus significant increase in the dose-corrected trough concentration after day 10.
		- effectiveness of TDM:
		  - decrease in trough concentration on day 3 by 26% (S; from 16.6 to 12.3 ng/mL), but no significant difference at the other time points.
		  - increase in the percentage of patients with a trough concentration < 10 ng/mL (lower limit of target value in early phase after transplantation) on day 3 by 180% (S; from 10% to 28%).
		  - decrease of the daily dose over the entire study period by 60% (after correction for age, gender and ethnicity) and by 68% after addition of ABCB1 genotype to the model (S).
		- no significant difference in the incidence of acute rejection confirmed by biopsy (NS; from 16% to 8%).
		- no significant difference in general 1-year survival (NS; from 99.1% to 92.3%).
		- no significant difference in loss of transplant in the surviving patients (NS; from 2.7% to 0%).
		- no significant differences in renal function (creatinine clearance) (NS).
		- no significant difference in the incidence of delayed transplant functioning (need for dialysis during the first week after transplantation) (NS; from 18.2% to 19.2%).
		- no significant increase in the incidence of diarrhoea (NS; from 20.9% to 34.6%).
		- no significant differences in liver function (serum concentrations of albumin and alanine amino transferase) (NS). There was a decrease in the serum albumin concentrations by 5% only after 3 months (S; from 43.3 to 41.1 g/L).
		
		*1/*1 compared to *3/*3:
		- decrease of the dose-corrected trough concentration over the entire study period by 27% (after correction for age, gender and ethnicity and after addition of ABCB1 genotype to the model) (NS).
		
		The authors report that a clinical trial is ongoing in which patients in the experimental arm receive an initial dose of tacrolimus that is based on the CYP3A5 genotype. They indicate that genotyping of CYP3A5 could play a role in reducing the late loss of a transplant through reducing the adverse events of nephrotoxicity and hypertension.
			Authors' conclusion:
			"We conclude that patients expressing CYP-3A5 need more tacrolimus to reach target concentrations and have a lower tacrolimus exposure shortly after transplantation. This delay in reaching target concentrations, however, did not result in an increased incidence of early biopsy proven acute rejection and therefore, genotyping for CYP3A5 is unlikely to improve short-term transplantation outcome."

ref. 26 Kuypers DR et al. CYP3A5 and CYP3A4 but not MDR1 single-	3	The tacrolimus concentration-time curves were determined after 7 days, 3 and 6 months and 1, 2, 3, 4 and 5 years in 95 kidney transplant patients (15x *1/*3, 80x *3/*3) receiving immunosuppressive treatment with tacrolimus, mycophenolate mofetil and a low dose oral methylprednisolone. Tacrolimus was started on the day of the transplant at a loading dose of 0.1 mg/kg twice daily, after which the dose	Authors' conclusion: "The lack of a time-related increase in dose-corrected tacro-

nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. Clin Pharmacol Ther 2007;82:711-25. **ref. 26, continuation**	*1/*3: D	was adjusted to achieve a trough concentration in the blood of 8 - 15 ng/mL during year 1 and 6 - 10 ng/mL after year 1. Chronic use of medication, which affects the absorption, distribution, metabolism or excretion of tacrolimus, was excluded, as was the use of inhibitors or inducers of CYP3A4. *1/*3 compared to *3/*3: - a significant increase in the weight-corrected daily dose at each time-point by 57 - 131% (S). - a significant decrease in $AUC_{0\text{-}12h}$[a] at each time-point except 2 years by 44 - 61% (S). The decrease on day 7 was 44% (S). - no significant increase in $AUC_{0\text{-}12h}$[a] versus a significant increase in $AUC_{0\text{-}12h}$[a] by 92% over 5 years (S; from 41.7 to 80 ng.h/mL per mg). - effectiveness of TDM: - no significant differences in the trough concentration at any time-point from day 7. - decrease in the trough concentrations during the first 6 days post-transplantation in a sub-group of *1/*3 with the CYP3A4*1B allele (n = 7) (S) and an increase in the time required to achieve a minimum trough concentration of 10 ng/mL by 200% (S; from 1.4 to 4.2 days), but no significant difference in the time to the first rejection episode confirmed by biopsy (NS; from 6.4 to 5.0 days). Similar results were found for the rest of the *1/*3 group, but the trough concentration was not significantly lower for days 4 - 6. - increase in the incidence of tacrolimus-related nephrotoxicity confirmed by biopsy by 257% (NS; from 11.2% to 40%). The mean $AUC_{0\text{-}12h}$ did not differ significantly between patients with and without nephrotoxicity. - no significant difference in the incidence of developing diabetes mellitus (NS; from 10% to 7%). - no significant difference in the incidence of developing hyperlipidaemia (NS; from 61.7% to 46.2%). - decrease in the incidence of hypertension in a subgroup of *1/*3 with the CYP3A4*1B allele (n = 7) by 55% (S; from 73.5% to 33.3%), but not in the rest of the group (NS; from 73.5% to 71.4%). - no significant differences in the incidence of the first episode of acute rejection confirmed by biopsy in the first 2 weeks (NS; from 16.2% to 20.0%) of or the total incidence of acute rejection during 5 years (NS; from 22.5% to 20.0%). The authors postulate that CYP3A5 in the kidney increases the risk of developing nephrotoxicity, possibly through an increase in the intrarenal concentration of potentially toxic metabolites of tacrolimus.	limus exposure observed with the CYP3A4*1/ CYP3A5*1 and CYP3A4*1B/CYP 3A5*1 genotypes is associated with tacrolimus-related nephrotoxicity, possibly as a result of higher concentrations of toxic metabolites." AUC^{a} compared to *3/*3 on day 7: *1/*3: 56%
ref. 27 Renders L et al. CYP3A5 genotype markedly influences the pharmacokinetics of tacrolimus and sirolimus in kidney transplant recipients. Clin Pharmacol Ther 2007;81:228-34.	3 *1/*3 + *1/*1: A	The tacrolimus trough concentrations were determined approx. 2 years after transplantation in 134 stable kidney transplant patients (3x*1/*1, 15x *1/*3, 116x *3/*3) on maintenance therapy with tacrolimus (usually in combination with mycophenolate mofetil (19% of the patients), prednisolone (30%), or both (44%)). $AUC_{0\text{-}12h}$, $t_{1/2}$ and Cl_{or} were determined in 16 patients (1x*1/*1, 6x *1/*3, 9x *3/*3). Tacrolimus was dose-adjusted according to the trough concentrations and the dose varied from 1 - 40 mg/day. Use of CYP3A substrates was not excluded. (*1/*3 + *1/*1) compared to *3/*3: - decrease in the dose-corrected trough concentration by 51% (S; from 1.49 to 0.74 $x10^{-3}$/L). - decrease in $AUC_{0\text{-}12h}$[a] by 60% (S; from 58.3 to 23.4 h.ng/mL). - increase in Cl_{or} by 210% (S; from 19.5 to 60.5 mL/h). - no significant decrease in $t_{1/2}$ (NS; from 12.3 to 9.1 h). - effectiveness of TDM: no significant differences in trough concentration and $AUC_{0\text{-}12h}$ (NS). - no significant increase in serum creatinine concentrations (NS; from 1.54 to 1.78 mg/dL).	Authors' conclusion: "Therefore, CYP-3A5 expressor status and not transporter variants is a main determinant of oral clearance, particularly for tacrolimus. Dose adaptation according to trough levels, however, appears to be sufficient to maintain similar concentration–time profiles."

ref. 27, continuation	*1/*3: A *1/*1: A	*1/*3 compared to *3/*3: - decrease in the dose-corrected trough concentration by 39% (S for the trend; from 1.49 to 0.91 x10^{-3}/L). *1/*1 compared to *3/*3: - decrease in the dose-corrected trough concentration by 76% (S for the trend; from 1.49 to 0.36 x10^{-3}/L). *1/*1 versus *1/*3 versus *3/*3: - association of the CYP3A5 genotype with the dose-corrected trough concentration (S; 0.36 versus 0.91 versus 1.49 x10^{-3}/L).	trough concentration[a] compared to *3/*3: *1/*3 61% *1/*1: 34%
ref. 28 Mourad M et al. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. Clin Chem Lab Med 2006;44:1192-8.	4 *1/*3 + *1/*1: A	The trough concentrations after the first dose of tacrolimus were determined in 59 kidney transplant patients (1x*1/*1, 9x *1/*3, 49x *3/*3) who were treated with tacrolimus in combination with azathioprine (1 mg/kg per day) or mycophenolate mofetil (500 mg twice daily) and methylprednisolone (500 mg on the day of transplantation, followed by a gradual reduction of the dose). Renal function was determined after 7 and 14 days. Tacrolimus was started on the day of the transplant (0.1 mg/kg twice daily oral), after which the dose was adjusted to achieve a trough concentration of 5 - 15 ng/mL. Use of medication that affects the absorption and metabolism of tacrolimus was excluded. (*1/*3 + *1/*1) compared to *3/*3: - decrease in the dose-corrected and weight-corrected trough concentration by 46% (S; from 209.6 to 113.3 ng.mg/mL per kg). - decrease in the percentage of patients with tacrolimus concentrations above the therapeutic range (> 15 ng/mL) by 69% (S; from 65% to 20%). - no significant differences in weight-corrected dose (NS). - the presence of at least one *1 allele formed a significant independent variable that affected the dose-corrected and weight-corrected blood concentrations (S). - the tacrolimus concentration on day 1 was not associated with the glomerular filtration speed and the serum creatinine concentration on days 7 and 14 (NS). Six patients with acute tubular necrosis who required haemodialysis after the transplantation were excluded from this analysis. No episodes of acute rejection occurred during the 1st month after transplantation.	Authors' conclusion: "Prospective trials are needed to prove that a genetic approach to tacrolimus pharmacokinetics and its related adverse events during the early period after grafting may improve patient outcome."
ref. 29 Roy JN et al. Cyp3A4, Cyp3A5, and MDR-1 genetic influences on tacrolimus pharmacokinetics in renal transplant recipients. Pharmacogenet Genomics 2006;16:659-65.	3 *1/*3 + *1/*1: A	In a prospective study, the tacrolimus trough concentrations were determined at two time-points (days 3 - 7 and after 3 months) in 44 kidney transplant patients (9x no *3/*3, 35x *3/*3), who were treated with tacrolimus (dose based on a trough concentration of 10 - 12 ng/mL), myco-phenolate mofetil and steroids. Follow-up for acute rejection and creatinine clearance was 3 months. The use of medication that could affect tacrolimus concentrations was excluded during the first week after transplantation. (no *3/*3) compared to *3/*3: - decrease in the dose-corrected and weight-corrected trough concentration by 65% after both 3 - 7 days and after 3 months (S; from 81.3 to 28.2 ng.mg/mL per kg and from 117.5 to 40.7 ng.mg/mL per kg respectively). - increase in the percentage of patients with a dose-corrected and weight-corrected trough concentration below the median (77.9 ng.mg/ mL per kg) (S; from 37% to 90%; OR_{corr} = 10.1). - the *3 allele was a significant variable that affected the dose-corrected and weight-corrected blood concentrations (S). - effectiveness of TDM: increase in the time required to achieve the target concentration (10 - 12 ng/mL) by 216% (S; from 3.8 to 12.0 days). - no significant increase in the incidence of acute rejection confirmed by biopsy during the first 3 months (NS; from 23% to 33%).	Authors' conclusion: "The complete absence of Cyp-3A5*3 allele and the accumulation of less than three copies of MDR-1 (T-129C, C3435T and G2677T) polymorphisms are associated with lower tacrolimus blood levels identifying these genotypes as markers for patients requiring higher tacrolimus doses."

ref. 29, continuation		- no significant differences in creatinine clearance after 3 months (NS; from 0.71% to 0.69 µL/min). A part of the *3/*3 group had low dose-corrected and weight-corrected trough concentrations. Two CYP3A5 alleles can be present on the same chromosome. Six patients with *3/*3 also had a third CYP3A5 allele (1x *6 and 5x *1C, 3 of which had low corrected trough concentrations). NOTE: Except for *3 (frequency of 84.1%), genotyping was also performed for *1B, *1C, *2, *5, *6 and SNP31611 in the 3'-UTR.*1B, *2 and *5 were not found in this Canadian population group. The frequency of *1C, *6 and SNP31611 in the 3'-UTR was 5.7%, 1.1% and 4.5% respectively. NOTE: Considering that most other studies only genotyped for *3, no *3/*3 in this study is equivalent to (*1/*1 + *1/*3) in the other studies.	
ref. 30 Cheung CY et al. Influence of different allelic variants of the CYP3A and ABCB1 genes on the tacrolimus pharmacokinetic profile of Chinese renal transplant recipients. Pharmacogenomics 2006;7:563-74.	4 *1/*1: A *1/*3: A	At an average 2.7 years after transplantation, the $AUC_{0\text{-}12h}$ for tacrolimus was determined based on the blood concentration at 2 and 4 hours after taking tacrolimus in 103 kidney transplant patients (10x *1/*1, 38x *1/*3, 55x *3/*3) who were being treated with tacrolimus in combination with azathioprine (n = 78) or mycophenolate mofetil (n = 25) and prednisolone. Tacrolimus was started at a dose of 0.15 mg/kg twice daily, after which the dose was adjusted to achieve a $AUC_{0\text{-}12h}$ value of 100 - 150 ng.h/mL during the first 3 months and 80 - 100 ng.h/mL thereafter. Use of co-medication and nutritional supplements and the presence of conditions that can affect tacrolimus concentrations were excluded. The prednisolone dose had no significant effect on the variation in tacrolimus dose. *1/*1 compared to *3/*3: - decrease in $AUC_{0\text{-}12h}^{ab}$ by 57% (S; from 2,143 to 920 ng.mg.h/mL per kg). - increase in the weight-corrected dose by 80% (S; from 0.050 to 0.090 mg/kg per day). *1/*3 compared to *3/*3: - decrease in $AUC_{0\text{-}12h}^{ab}$ by 47% (S; from 2,143 to 1,228 ng.mg.h/mL per kg). - increase in the weight-corrected dose by 40% (S; from 0.050 to 0.070 mg/kg per day). *1/*1 versus *1/*3 versus *3/*3: - the CYP3A5*3 polymorphism was the most important significant independent variable and explained 35% of the variability in required dose (S).	Authors' conclusion: "The CYP3A5*3 polymorphism may be an important factor in determining the dose requirement for tacrolimus and genotyping can help determine the initial daily dose required by individual patients for adequate immunosuppression." AUC^{ab} compared to *3/*3 after on average 2.7 years: *1/*3: 53% *1/*1: 43%
ref. 31, liver Uesugi M et al. Effect of intestinal CYP3A5 on postoperative tacrolimus trough levels in living-donor liver transplant recipients. Pharmacogenet Genomics 2006;16:119-27.	3 *1/*1: A *1/*3: A	The median dose-corrected trough concentration was determined in week 1, week 2, week 3, week 4 and week 5 after transplantation in 201 liver transplant patients (9x*1/*1, 63x *1/*3, 129x *3/*3) on immunosuppressive therapy with tacrolimus (dosed at a trough concentration of 5 - 15 ng/mL). *1/*1 compared to *3/*3: - decrease in the median dose-corrected trough concentration by 41 - 62% (S for weeks 1 - 4). *1/*3 compared to *3/*3: - decrease in the median dose-corrected trough concentration (S for weeks 1 - 5), but decrease is less than for *1/*1. *1/*1 compared to *3/*3: - non-significant decrease in the median dose-corrected trough concen-tration in weeks 1 - 5 (NS). The dose-corrected trough concentration decreased over time. For patients with *1/*1 or *1/*3, the CYP3A5 genotype of the	Authors' conclusion: "These results indicate that intestinal CYP3A5, as well as hepatic CYP3A5, plays an important role in the first-pass effect of orally administered tacrolimus."

ref. 31, continuation		transplant affected the dose-corrected trough concentration significantly.	
ref. 32 Zhang X et al. Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation. Clin Transplant 2005;19:638-43.	3 *1/*1: A *1/*3: A	The tacrolimus trough concentration was determined 1 week, 1 month and 3 months after transplantation in 118 kidney transplant patients (12x*1/*1, 36x *1/*3, 70x *3/*3) on immunosuppressive treatment with tacrolimus, mycophenolate mofetil and corticosteroids. Tacrolimus was started at a dose of 0.075 mg/kg twice daily, after which the dose was adjusted to achieve a trough concentration in the blood of 10 ng/mL during the first 3 months and 5 ng/mL thereafter. Use of co-medication that affects the concentration of tacrolimus was excluded. *1/*1 compared to *3/*3: - decrease in the weight-corrected and dose-corrected trough concentration by 68% after 1 week and 1 month and 77% after 3 months (S). *1/*3 compared to *3/*3: - decrease in the weight-corrected and dose-corrected trough concentration by 59% after 1 week, 55% after 1 month and 61% after 3 months (S). *1/*1 compared to *3/*3: - decrease in the weight-corrected and dose-corrected trough concentration by 21% after 1 week (NS), 29% after 1 month (S) and 40% after 3 months (S). *1/*1 versus *1/*3 versus *3/*3: - effectiveness of TDM: - increase in the trough concentration with the number of *3 alleles, both after 1 week and after 1 and 3 months (S). This suggests a much poorer TDM in this study than in other studies, in which the target concentration was achieved much sooner after transplantation. - after 1 week, 46% of (*1/*1 + *1/*3) had trough concentrations < 5 ng/mL and 77% had trough concentrations < 8 ng/mL, whilst 10% of *3/*3 had a trough concentration > 20 ng/mL.	Authors' conclusion: "CYP3A5*1/*3 polymorphisms are associated with tacrolimus pharmacokinetics and dose requirements in renal transplant recipients. Pharmacogenetic methods could be employed prospectively to help initial dose selection and to individualize immunosuppressive therapy." Trough concentration[ab] compared to *3/*3 after 1 week: *1/*3: 41% *1/*1: 32%
ref. 33 Tada H et al. Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant Proc 2005;37:1730-2.	3 *1/*1 + *1/*3: A	The pharmacokinetic parameters of tacrolimus were determined 4 weeks after transplantation in 39 kidney transplant patients (1x*1/*1, 16x *1/*3, 22x *3/*3) on immunosuppressive treatment with tacrolimus, mycophenolate mofetil and corticosteroids. (*1/*1+ *1/*3) compared to *3/*3: - decrease in $AUC_{0\text{-}12h}$[ab] by 34% (S; from 0.865 to 0.570 ng.mg.h/mL per kg). - increase in Cl_{or} by 39% (S; from 25.1 to 35.0 L/h). - non-significant decrease in $t_{1/2}$ by 31% (NS). - effectiveness of TDM: no significant differences in $AUC_{0\text{-}12h}$ and trough concentration.	Authors' conclusion: "Renal transplant recipients who were CYP3A5*1 carriers required a higher dose of tacrolimus than CYP3A5*3/*3, indicating a significantly lower dose-adjusted $AUC_{0–12}$ of tacrolimus."
ref. 34 Macphee IA et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and	3	A total of 180 kidney transplant patients, of which 169 were White (16x (*1/*1 + *1/*3), 103x *3/*3), 26 South Asian (17x (*1/*1 + *1/*3), 9x *3/*3), 23 Black (20x (*1/*1 + *1/*3), 3x *3/*3) and 12 had Middle Eastern ancestors (3x (*1/*1 + *1/*3), 9x *3/*3), received tacrolimus and cortico-steroids and some also received a third medication (azathioprine, n = 45 or mycophenolate mofetil, n = 26). Tacrolimus dose was adjusted to achieve a trough concentration of 10 - 15 ng/mL. (*1/*1+ *1/*3) compared to *3/*3: - decrease in the weight-corrected and dose-corrected trough concentration 3 months after transplantation by a factor of 2 for White and South Asian patients (S). The decrease was non-	Authors' conclusion: "Genotyping for CYP3A5*1 to identify CYP3A5 expressors has the potential to identify individuals with a high dose requirement for tacrolimus and may be a useful tool for

South Asians. Transplantation 2005;79:499-502. **ref. 34, continuation**	*1/*1 + *1/*3: B	significant for the two smallest groups (Black and Middle Eastern). - effectiveness of TDM: - decrease in the mean trough concentration in week 1 and week 2 after transplantation by 26% and 21% respectively (S; from 18.4 to 13.6 ng/mL and from 14.3 to 11.2 ng/mL respectively). - increase in the time required to achieve the target concentration (10 - 15 ng/mL): - increase in the percentage of patients with the mean trough concentration outside the target range in week 1 by 379% (S; from 8.2% to 39.3%) and in week 2 by 139% (S; from 3.3% to 17.9%). - increase in the percentage of White patients with the mean trough concentration outside the target range in week 1 by 782% (S; from 7.8% to 68.8%) and in week 2 by 382% (S; from 3.9% to 18.8%). - decrease in the percentage of patients with at least 1 trough concentration > 20 ng/mL in week 1 by 46% (S; from 73.0% to 39.3%). - no significant difference in the incidence of first episodes of acute rejection confirmed by biopsy during the first 3 months (NS; from 43% to 41%), but there was a decrease in the average time to the first period of rejection by 38% (S; from 13 to 8 days).	individualizing immunosuppressive drug treatment."
ref. 35 Hesselink DA et al. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther 2003;74:245-54.	3 *1/*3: A *1/*1 + *1/*3: A	Data were analysed for 62 kidney transplant patients (2x *1/*1, 15x *1/*3, 45x *3/*3) who had received their transplant more than 1 year ago and were receiving immunosuppressive treatment with tacrolimus. Use of medication that affects the absorption and metabolism of tacrolimus was excluded. *1/*3 compared to *3/*3: - decrease in the mean weight-corrected and dose-corrected trough concentration 3 and 12 months after transplantation by 35% and 54% respectively (S; from 94.4 to 61.0 ng.mg/mL per kg and from 124.2 to 57.6 ng.mg/mL per kg respectively). - effectiveness of TDM: no significant differences in the trough concentrations. (*1/*1+ *1/*3) compared to *3/*3: - decrease in the median weight-corrected and dose-corrected trough concentration 3 months after transplantation by 35% (S; from 94.4 to 61.0 ng.mg/mL per kg). The decrease was also significant in the subgroup of White patients (77%). - effectiveness of TDM: no significant differences in the trough concentrations. - no significant difference in the incidence of acute rejection confirmed by biopsy (NS; from 20.0% to 23.5%), but these were patients with a transplant survival ≥ 1 year and no severe medication toxicity that necessitated suspension of tacrolimus. NOTE: In addition to *3, genotyping was also performed for *6, but the two *1/*6 patients that were found were excluded from the analysis, because it was not clear whether the *1 and *6 polymorphisms occurred on the same chromosome.	Authors' conclusion: "As a group, patients with the CYP3A5*3/*3 genotype require less tacrolimus to reach target predose concentrations compared with CYP3A5*1 allele carriers." Median trough concentration[ab] compared to *3/*3 after 3 months: *1/*3: 65%

[a] Corrected for the dose.
[b] Corrected for body weight.
AA[# t] the genotype has a significant effect, but this effect is favourable instead of unfavourable and therefore does not require any action for this genotype.

Risk group	-

Comments:

For the period after March 2015, studies involving more than 400 patients with a liver transplant or more than 600 patients with another indication were only included if they investigated clinical endpoints. Studies with

genotype-guided dosing were only included if more than 100 patients received genotype-guided dosing. Kinetic studies were only included if they involved at least 60 CYP3A5 expressers.
For the period starting October 2008, only studies involving more than 400 patients with a liver transplant or more than 500 patients with another indication, and studies with genotype-guided dosing were included. Furthermore, kinetic results were only included if the data were determined per genotype (i.e. for *1/*1 and *1/*3 separately). In addition to this, a study was included that examined the link between improvement of the number of patients with a concentration within the target range on day three and clinical outcomes. Other articles did not contribute sufficiently to the burden of proof. Jacobson PA et al. Novel polymorphisms associated with tacrolimus trough concentrations: results from a multicenter kidney transplant consortium. Transplantation 2011;91:300-8. PubMed PMID: 21206424 was not included, because it concerns the same study as Pulk 2015 and provides data for fewer patients.
Due to the large number of articles about CYP3A5 and tacrolimus (36 relevant references as of 15 October 2008), a selection was made for the risk analysis. This selection took place according to the following criteria:
- studies involving patients, no studies involving volunteers.
- all studies with clinical effects (other than doses)
- genotyping for CYP3A5 (and not for CYP3A1, which exhibits a strong linkage with CYP3A5).
- kinetic studies with ≥ 15x (*1/*1 + *1/*3) and ≥ 15x *3/*3
- kinetic studies with transplantations other than liver transplantation, as in the case of liver transplantation the plasma concentration of tacrolimus is not only affected by the genotype of the patient, but also by the genotype of the transplant. To illustrate this, the largest kinetic study following liver transplantation was included (in addition to a study that also examined a clinical effect).

- Dose recommendations from the literature (dosing algorithms and dosing equations based on modelling only included before 2015):
  - Birdwell KA et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. Clin Pharmacol Ther 2015;98:19-24.
    For both *1/*3 and *1/*1 the authors recommend an initial dose that is 1.5 - 2 times higher than the normal initial dose. The total initial does may not exceed 0.3 mg/kg per day. The dose must be adjusted according to TDM.
    The dose recommendation applies to patients with kidney, heart, lung and stem cell transplants and for liver transplant patients where the genotype of the transplant is identical to that of the patient. The evidence supporting the dose recommendation is strong.
    The authors indicate that co-medication - particularly verapamil, diltiazem and triazole derivatives - must be taken into consideration when setting the dose. The interaction with triazole derivatives is monitored via the interaction database. In addition to this, the authors indicate that patient factors such as fasting and diarrhoea can affect tacrolimus metabolism.
    The guideline above was still the most recent version on the website of CPIC on 10 April 2024.
  - Passey C et al. Dosing equation for tacrolimus using genetic variants and clinical factors. Br J Clin Pharmacol 2011;72:948-57.
    Based on the data from 681 kidney transplant patients (Jacobson PA et al. Novel polymorphisms associated with tacrolimus trough concentrations: results from a multicenter kidney transplant consortium. Transplantation 2011;91:300-8. PubMed PMID: 21206424, which is a substudy from Pulk 2015), the authors postulated the following dose algorithm:
    the total daily dose (mg) = 0.9216 x the target value for the tacrolimus trough concentration (ng/mL) x [(0.86, if day 6 - 10 after transplantation) or (0.71, if day 11 - 180 after transplantation)] x [(1.69, if CYP3A5 *1/*3) or (2.00, if CYP3A5*1/*1)] x (0.70, if treatment takes place in a steroid sparing centre) x [(age in years/50)$^{-0,4}$] x (0.94, if the patient is taking a calcium antagonist)

Date of literature search: 11 March 2024.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	homozygous expresser	4 E	Yes	Yes	23 May 2024
	heterozygous expresser	4 E	Yes	Yes	

Mechanism:
Tacrolimus is primarily converted to metabolites by CYP3A4 and CYP3A5 and these metabolites do not contribute to the pharmacological activity of tacrolimus. CYP3A5 can metabolise tacrolimus in the liver, intestines and kidneys.