Supplemental To: Prospective *CYP2C19*-Guided Voriconazole Prophylaxis in Neutropenic AML Patients Reduces the Incidence of Subtherapeutic Antifungal Plasma Concentrations

Table S1. Characteristics of the entire patient cohort stratified by *CYP2C19* diplotypes (n=263)

	CYP2C19*17/*17 **n=5**	***CYP2C19*1/*17*** **n=74**	***CYP2C19*1/*1*** **n=105**	***CYP2C19*2/*17*** **n=23**	***CYP2C19*1/*2*** **n=49**	***CYP2C19*2/*2*** **n=7**	***p***
Age (years)							
Median	69	67	63	68	64	52	
Range	60-71	24-85	19-81	31-79	22-86	33-67	0.04
Sex							
Female	0	38	57	4	21	4	
Male	5	36	48	19	28	3	0.004
Weight (kg)							
Median	93.8	83.8	81.4	78.9	76.4	69.3	
Range	65.8-106.8	47.5-129.9	38-165.8	50.9-123.6	48-112.8	51.3-118.4	0.36

Statistical analysis for continuous variables (i.e., age and weight) was performed by the Kruskal Wallis test, and for categorical variables (i.e., sex) the Fisher's exact test. *CYP2C19*17/*17* and *CYP2C19*2/*17* diplotype groups had a greater number of males than females. *CYP2C19*2/*2* diplotype group had a younger median age when compared to the other *CYP2C19* diplotype groups. When stratifying patients by phenotype (i.e., ultrarapid metabolizers (*CYP2C19*17/*17*), rapid metabolizers (*CYP2C19*1/*17*), normal metabolizers (*CYP2C19*1/*1*), intermediate metabolizers (*CYP2C19*2/*17*, *CYP2C19*1/*2*), poor metabolizers (*CYP2C19*2/*2*)), only sex is significantly different (p=0.01) among the phenotypes. The differences in age and sex among the diplotype groups and sex among phenotype groups are not predicted to influence study outcomes.

Table S2. Characteristics of the 202 patients receiving prophylactic voriconazole

Age	
Median (years)	64
Range (years)	19-85
Sex	**No. (%)**
Female	99 (49.0)
Male	103 (51.0)
Weight	
Median (kg)	80.7
Range (kg)	42-165.8
Self-declared race	**No. (%)**
Asian	7 (3.5)
Black	11 (5.5)
Other	12 (5.9)
Unknown	19 (9.4)
White	153 (75.7)
***CYP2C19* diplotypes/phenotypes**	**No. (%)**
*CYP2C19*17/*17*–ultrarapid metabolizer	4 (2.0)
*CYP2C19*1/*17*–rapid metabolizer	58 (28.7)
*CYP2C19*1/*1*–normal metabolizer	75 (37.1)
*CYP2C19*2/*17*–intermediate metabolizer	16 (7.9)
*CYP2C19*1/*2*–intermediate metabolizer	42 (20.8)
*CYP2C19*2/*2*–poor metabolizer	7 (3.5)

Table S3. Characteristics of the 202 patients receiving prophylactic voriconazole stratified by *CYP2C19* diplotypes

	CYP2C19*17/*17 **n=4**	***CYP2C19*1/*17*** **n=58**	***CYP2C19*1/*1*** **n=75**	***CYP2C19*2/*17*** **n=16**	***CYP2C19*1/*2*** **n=42**	***CYP2C19*2/*2*** **n=7**	***p***
Age (years)							
Median	66.5	66	62	67	63.5	52	
Range	60-71	24-85	19-81	31-79	22-75	33-67	0.17
Sex							
Female	0	30	43	2	20	4	
Male	4	28	32	14	22	3	0.007
Weight (kg)							
Median	89.1	85.6	81.4	79.1	76.8	69.2	
Range	65.5-106.8	47.5-129.9	42-165.8	50.9-123.6	52.6-112.8	51.3-118.4	0.34

Statistical analysis for continuous variables (i.e., age and weight) was performed by the Kruskal Wallis test, and for categorical variables (i.e., sex) the Fisher's exact test. *CYP2C19*17/*17* and *CYP2C19*2/*17* diplotype groups had a greater number of males than females. When stratifying patients by phenotype (i.e., ultrarapid metabolizers (*CYP2C19*17/*17*), rapid metabolizers (*CYP2C19*1/*17*), normal metabolizers (*CYP2C19*1/*1*), intermediate metabolizers (*CYP2C19*2/*17*, *CYP2C19*1/*2*), poor metabolizers (*CYP2C19*2/*2*)), there are no significant differences among the phenotypes. The differences in age among diplotype groups are not predicted to influence study outcomes.

Table S4. Characteristics of the 70 patients with voriconazole plasma trough concentrations

Age	
Median (years)	64.5
Range (years)	24-79
Sex	**No. (%)**
Female	36 (51.4)
Male	34 (48.6)
Weight	
Median (kg)	79.3
Range (kg)	42-127.4
Self-declared race	**No. (%)**
Black	1 (1.4)
Asian	4 (5.7)
Other	4 (5.7)
Unknown	4 (5.7)
White	57 (81.4)
***CYP2C19* diplotypes/phenotypes**	**No. (%)**
*CYP2C19*1/*17*–rapid metabolizer	41 (58.6)
*CYP2C19*1/*1*–normal metabolizer	13 (18.6)
*CYP2C19*2/*17*–intermediate metabolizer	4 (5.7)
*CYP2C19*1/*2*–intermediate metabolizer	7 (10.0)
*CYP2C19*2/*2*–poor metabolizer	5 (7.1)

Table S5. Characteristics of the 70 patients with voriconazole plasma trough concentrations stratified by *CYP2C19* diplotypes

	CYP2C19*17/*17 **n=0**	***CYP2C19*1/*17*** **n=41**	***CYP2C19*1/*1*** **n=13**	***CYP2C19*2/*17*** **n=4**	***CYP2C19*1/*2*** **n=7**	***CYP2C19*2/*2*** **n=5**	***p***
Age (years)							
Median	N/A	65	66	71.5	64	52	
Range	N/A	24-79	50-75	63-76	24-69	33-67	0.1
Sex							
Female	N/A	23	6	0	3	4	
Male	N/A	18	7	4	4	1	0.18
Weight (kg)							
Median	N/A	82.9	75.9	78.1	71.2	69.2	
Range	N/A	47.5-127.4	42-107.7	66-103	62.6-96.7	51.3-118.4	0.56

Statistical analysis for continuous variables (i.e., age and weight) was performed by the Kruskal Wallis test, and for categorical variables (i.e., sex) the Fisher's exact test. When stratifying patients by phenotype (i.e., rapid metabolizers (*CYP2C19*1/*17*), normal metabolizers (*CYP2C19*1/*1*), intermediate metabolizers (*CYP2C19*2/*17*, *CYP2C19*1/*2*), poor metabolizers (*CYP2C19*2/*2*)), there are no significant differences among the phenotypes.

Table S6. Characteristics of the 176 patients dosed per *CYP2C19* recommendations

Age	
Median (years)	64
Range (years)	19-81
Sex	**No. (%)**
Female	83 (47.2)
Male	93 (52.8)
Weight	
Median (kg)	80.5
Range (kg)	42-148.3
Self-declared race	**No. (%)**
Asian	6 (3.4)
Black	8 (4.5)
Other	9 (5.1)
Unknown	14 (8.0)
White	139 (79.0)
***CYP2C19* diplotypes/phenotypes**	**No. (%)**
*CYP2C19*17/*17*–ultrarapid metabolizer	3 (1.7)
*CYP2C19*1/*17*–rapid metabolizer	46 (26.1)
*CYP2C19*1/*1*–normal metabolizer	64 (36.4)
*CYP2C19*2/*17*–intermediate metabolizer	16 (9.1)
*CYP2C19*1/*2*–intermediate metabolizer	40 (22.7)
*CYP2C19*2/*2*–poor metabolizer	7 (4.0)

Table S7. Characteristics of the 176 patients dosed per *CYP2C19* recommendations stratified by *CYP2C19* diplotypes

	CYP2C19*17/*17 **n=3**	***CYP2C19*1/*17*** **n=46**	***CYP2C19*1/*1*** **n=64**	***CYP2C19*2/*17*** **n=16**	***CYP2C19*1/*2*** **n=40**	***CYP2C19*2/*2*** **n=7**	***p***
Age (years)							
Median	64	66	63	68	64	52	
Range	60-71	31-78	19-81	31-79	22-75	33-67	0.43
Sex							
Female	0	24	34	2	19	4	
Male	3	22	30	14	21	3	0.03
Weight (kg)							
Median	93.8	84.9	82	79.1	76.8	69.2	
Range	65.8-106.8	47.5-129.9	42-148.3	50.9-123.6	52.6-112.8	51.3-118.4	0.33

Statistical analysis for continuous variables (i.e., age and weight) was performed by the Kruskal Wallis test, and for categorical variables (i.e., sex) the Fisher's exact test. *CYP2C19*17/*17* and *CYP2C19*2/*17* diplotype groups had a greater number of males than females. When stratifying patients by phenotype (i.e., ultrarapid metabolizers (*CYP2C19*17/*17*), rapid metabolizers (*CYP2C19*1/*17*), normal metabolizers (*CYP2C19*1/*1*), intermediate metabolizers (*CYP2C19*2/*17*, *CYP2C19*1/*2*), poor metabolizers (*CYP2C19*2/*2*)), there are no significant differences among the phenotypes. The differences in age among diplotype groups are not predicted to influence study outcomes.

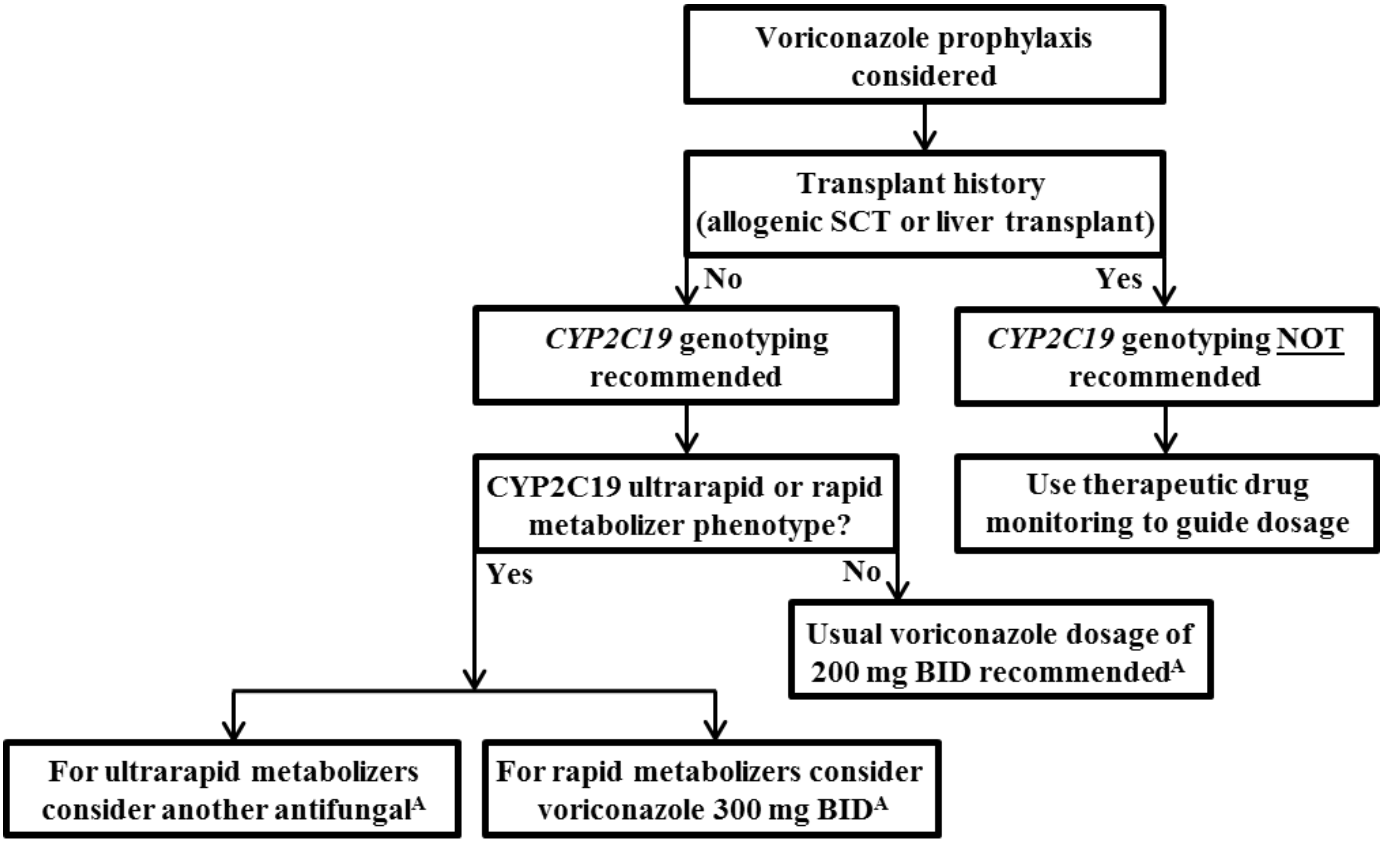
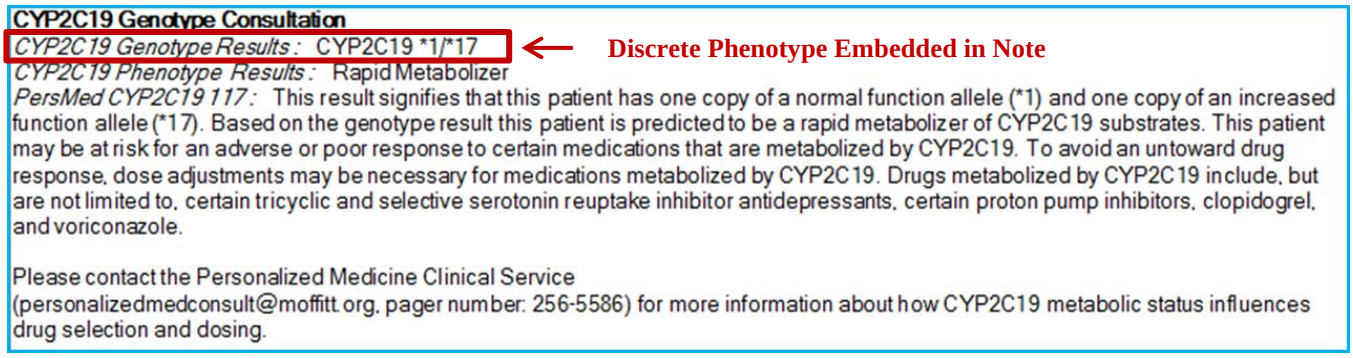


Figure S1: Schematic of clinical workflows for *CYP2C19* genotyping and voriconazole dosing. Alternative antifungal recommendations for CYPC19 ultrarapid metabolizers are based on formulary and Infectious Disease recommendations. For patients with a history of allogenic stem cell transplant, a pre-transplant germline DNA sample must be available for *CYP2C19* genotyping to be included in this quality improvement study. [A]Weight, concomitant drugs, and liver function may influence drug selection and dosage. SCT = stem cell transplant

A.

Personalized Medicine Notes and Data	
Personalized Medicine CYP2C19	Personalized Medicine CYP2C19
CYP2C19 Genotype Test Results	CYP2C19 *1/*17
CYP2C19 Phenotype Test Results	(A) (c) Rapid Metabolizer



CYP2C19 Genotype Consultation

CYP2C19 Genotype Results : CYP2C19 *1/*17 ← **Discrete Phenotype Embedded in Note**

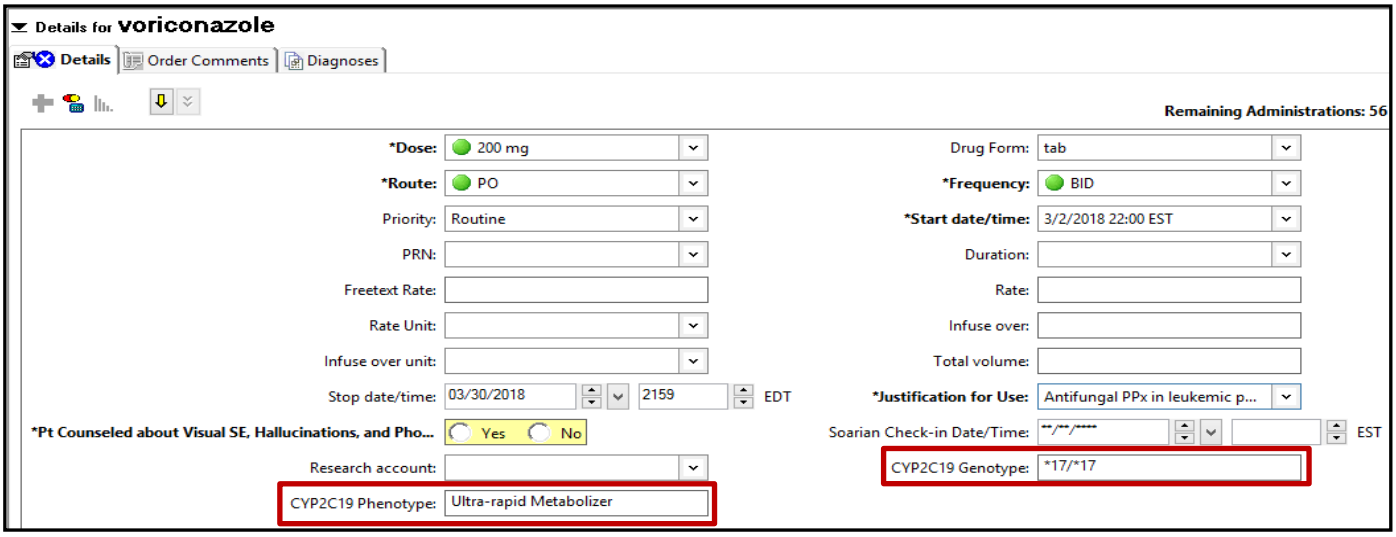
CYP2C19 Phenotype Results : Rapid Metabolizer

PersMed CYP2C19 117 : This result signifies that this patient has one copy of a normal function allele (*1) and one copy of an increased function allele (*17). Based on the genotype result this patient is predicted to be a rapid metabolizer of CYP2C19 substrates. This patient may be at risk for an adverse or poor response to certain medications that are metabolized by CYP2C19. To avoid an untoward drug response, dose adjustments may be necessary for medications metabolized by CYP2C19. Drugs metabolized by CYP2C19 include, but are not limited to, certain tricyclic and selective serotonin reuptake inhibitor antidepressants, certain proton pump inhibitors, clopidogrel, and voriconazole.

Please contact the Personalized Medicine Clinical Service (personalizedmedconsult@moffitt.org, pager number: 256-5586) for more information about how CYP2C19 metabolic status influences drug selection and dosing.

Figure S2: A) Screenshot of *CYP2C19* results displayed in the EHR. *CYP2C19* results are entered into the EHR in a textual, non-discrete manner. **B)** Screenshot of a semi-automated Personalized Medicine *CYP2C19* interpretation note that is entered into the EHR for every *CYP2C19* result. A discrete phenotype is embedded in the note for the purpose of driving clinical decision support alerts.

A.



B.

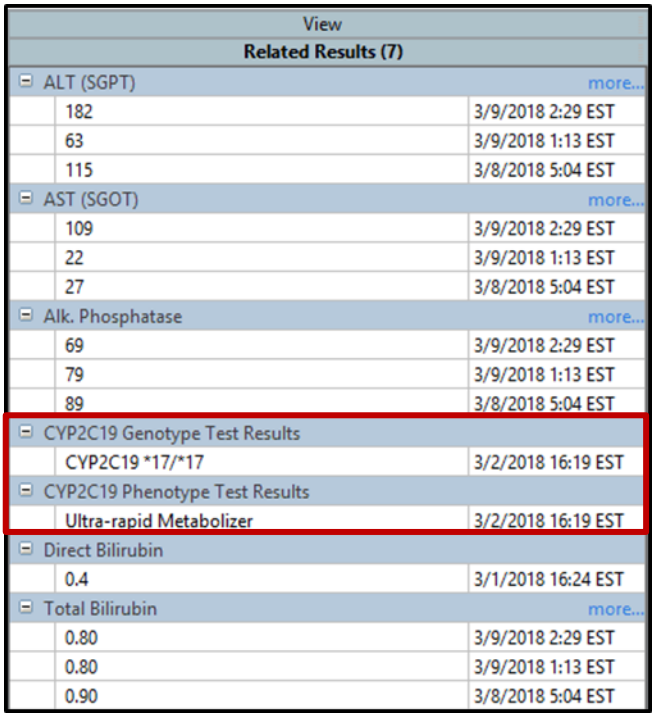
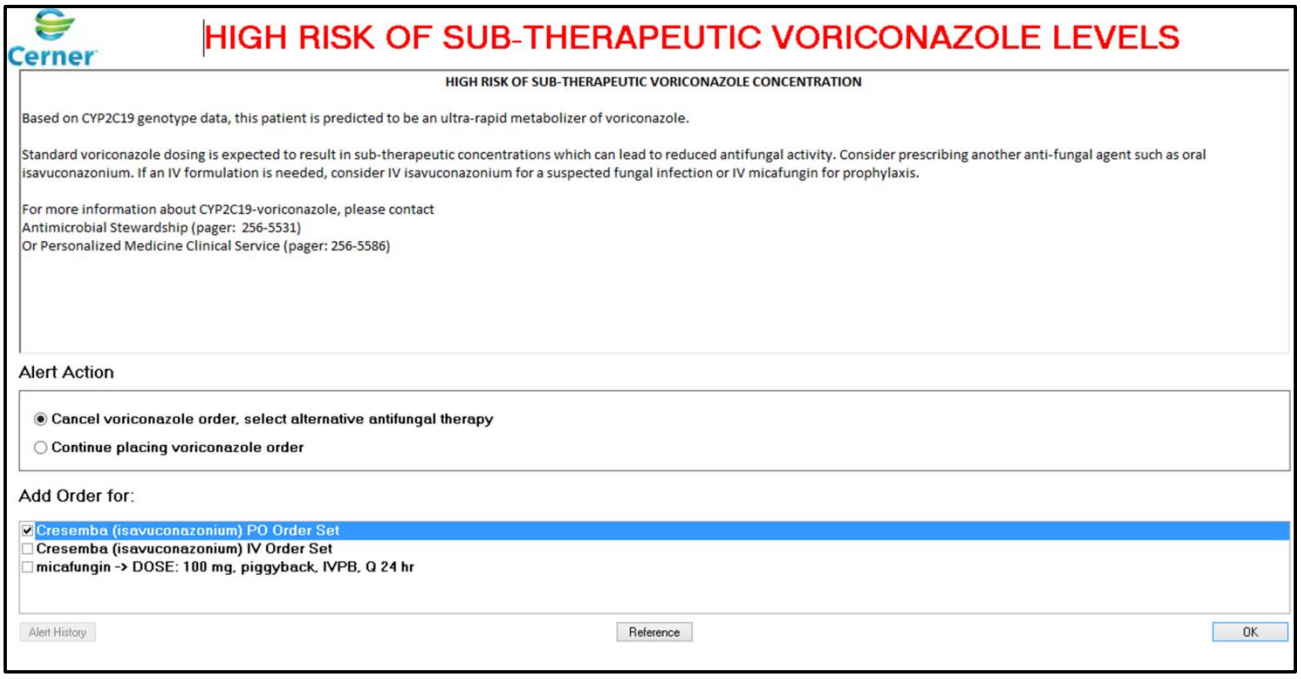


Figure S3: A) Screenshot of the Drug Order Field for voriconazole. Passive CDS consisting of the *CYP2C19* genotype and predicted phenotype are placed in the Drug Order Field to remind clinicians of important results. **B)** Screenshot of the Related Results section of the Drug Order Field. *CYP2C19* results are also included in the Related Results section, which consists of laboratory test results that may influence voriconazole dosing.

A.



B.

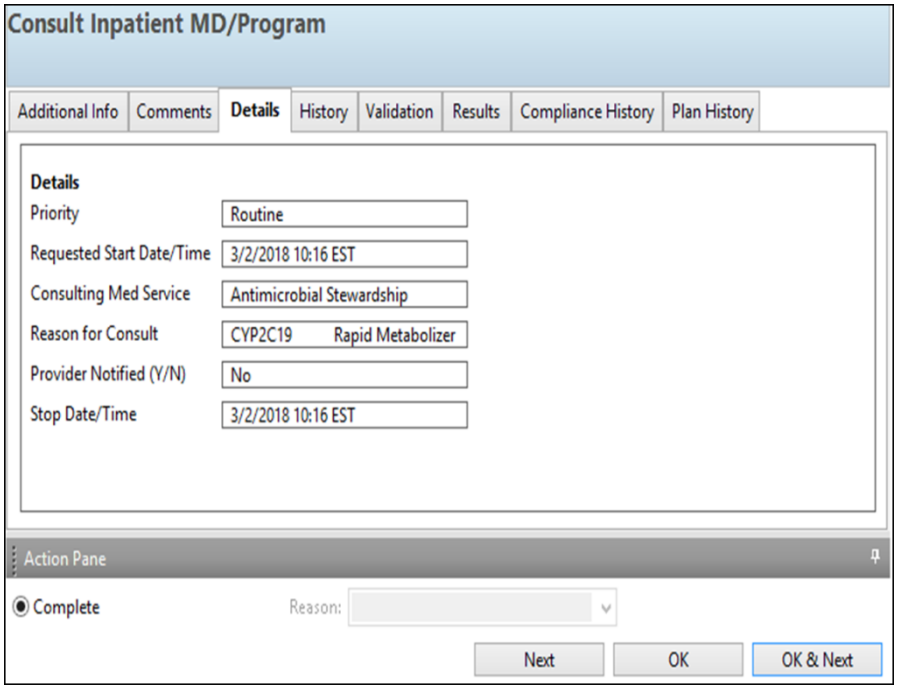


Figure S4: A) Screenshot of an interruptive, *CYP2C19*-voriconazole clinical decision support alert. Ordering voriconazole for a patient with a discrete CYP2C19 ultrarapid metabolizer phenotype curated in a Personalized Medicine interpretation note triggers alert firing. Selecting 'OK' automatically cancels the voriconazole order and initiates a loading dose order set for isavuconazonium. An education document (**Figure S5**) is available by clicking the 'reference' icon. **B)** Screenshot of an automated consult to the Antimicrobial Stewardship service. To help prevent alert fatigue at the point-of-care, an automated consult to the antimicrobial stewardship program, instead of a pop-up alert, is triggered when voriconazole is ordered for a patient with a rapid metabolizer status. The antimicrobial stewardship consult prompts review of voriconazole dosing.

MOFFITT PERSONALIZED MEDICINE CLINICAL SERVICE

CYP2C19 – VORICONAZOLE CLINICAL CONSIDERATIONS

Purpose of Document: CYP2C19 metabolizes voriconazole to compounds with less antifungal activity. Those with CYP2C19 rapid or ultra-rapid metabolism are at risk of low voriconazole concentrations. *CYP2C19* genotyping is offered at Moffitt Cancer Center (**test name CYP2C19 Genotype**) to help identify those predicted to be CYP2C19 ultra-rapid/rapid metabolizers. The purpose of this document is to provide guidance for *CYP2C19* test ordering, result interpretation, and gene-based pharmacotherapy recommendations.

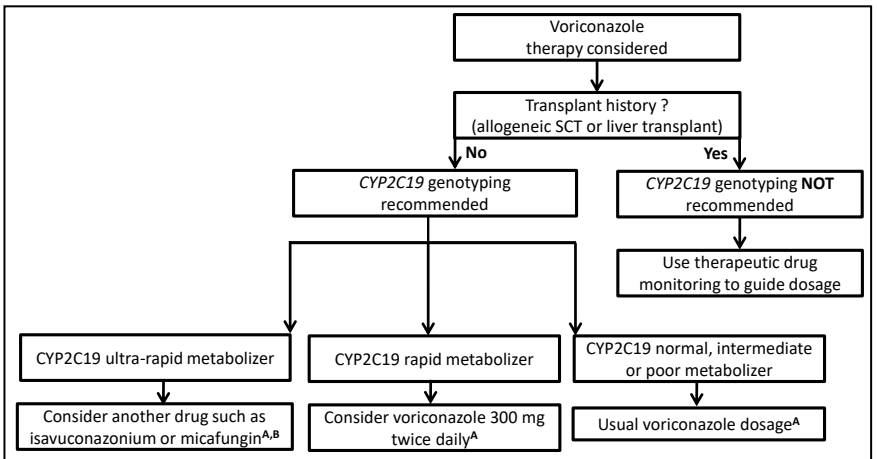


Figure 1. *CYP2C19* Genotyping-Voriconazole Algorithm. [A]Weight, concomitant drugs, and liver function may influence drug selection and dosage. [B]Oral isavuconazonium is preferred. If an IV drug formulation is warranted, consider IV isavuconazonium for suspected fungal infections or IV micafungin for prophylaxis.

***CYP2C19*–Voriconazole:** Genetic variations may influence the enzymatic activity of CYP2C19. **Table 1** provides possible *CYP2C19* genotype results along with predicted phenotypes (enzyme activity). Consideration should be given to *CYP2C19* genotyping to identify ultra-rapid or rapid metabolizers, who represent ~ 25% of the population. These individuals are at risk of sub-therapeutic voriconazole concentrations which can result in reduced antifungal activity.[1,2] Therapeutic modifications such as selecting a different drug or dosage (**Table 1**) may help prevent progressive fungal infections in a cost-effective manner.[3] An algorithm is available for clinical decision making regarding *CYP2C19*-voriconazole (**Figure 1**).

Voriconazole Therapeutic Drug Monitoring: Voriconazole has a narrow therapeutic range of 1-5.5 mcg/mL.[4,5] Voriconazole trough concentrations should be obtained at steady-state (5-7 days after starting therapy). For those with a trough <1 mcg/mL, the voriconazole dosage should be increased. If the voriconazole dose is increased and trough concentrations continue to be <1 mcg/mL, another antifungal agent should be considered.

CYP2C19 Based Pharmacotherapy Recommendations: There is strong evidence suggesting that ultra-rapid metabolizers should avoid voriconazole and that rapid metabolizers should be administered higher doses.[1-3] **Table 1** summarizes the pharmacotherapy recommendations based on CYP2C19 metabolizer status.

Table 1. Voriconazole dosing recommendations based on CYP2C19 phenotype[A]

***CYP2C19* result**	**CYP2C19 phenotype**	**Implications**	**Dosing recommendations**
**17/*17*	Ultra-rapid metabolizer	Very high risk of sub-therapeutic voriconazole concentrations	Consider oral isavuconazonium. If an IV formulation is warranted, consider IV isavuconazonium for suspected fungal infections or IV micafungin for prophylaxis.[A]
**1/*17*	Rapid metabolizer	High risk of sub-therapeutic voriconazole concentrations	Consider voriconazole 300 mg twice daily for prophylaxis or treatment.[A,B]
**1/*1*	Normal metabolizer	No influence on voriconazole plasma concentrations	Consider voriconazole 200 mg twice daily for prophylaxis or 300 mg twice daily for treatment.[A,B]
**1/*2, *1/*3, *2/*17, *3/*17*	Intermediate metabolizer	Risk of elevated voriconazole plasma concentrations	Consider voriconazole 200 mg twice daily for prophylaxis or 300 mg twice daily for treatment[A,B]
**2/*2, *3/*3, *2/*3*	Poor metabolizer	Risk of elevated voriconazole plasma concentrations	Consider voriconazole 200 mg twice daily for prophylaxis or treatment.[A,B]

[A]Weight, concomitant drugs, liver function, and prior voriconazole trough concentration may influence drug selection and dosage.
[B]Use therapeutic drug monitoring to guide dosage.

OTHER CONSIDERATIONS: For those individuals with a history of allogenic stem cell transplant, *CYP2C19* genetic test results may be representative of the donor genotype and not the host genotype. For those individuals with a history of liver transplant, *CYP2C19* genetic test results may not be representative of donor liver metabolic capacity. *CYP2C19* genotyping is not recommended for those with a history of allogenic stem cell transplant or liver transplant. Instead, use voriconazole therapeutic drug monitoring to guide dosage.

CYP2C19 genotyping turnaround time is approximately 5 days. For questions regarding who should be considered for *CYP2C19* genotyping or questions about drug therapy please contact the Personalized Medicine Clinical Service (pager 256-5586), the Antimicrobial Stewardship (256-5531) or a clinical pharmacist.

REFERENCES:

1. Hicks et al. *Pharmacogenomics*. 15, 2014 PMID: 25084200
2. Lamoureux et al. *Int J Antimicrob Agents*. 47, 2016 PMID: 26775563
3. Mason et al. *J Antimicrob Chemother*. 70, 2015 PMID: 26233624
4. Mitsani et al. *Antimicrob Agents Chemother.* 56, 2012 PMID:22330924
5. Trifilio et al. *Bone Marrow Transplant*. 40, 2007 PMID: 17589527

Figure S5: *CYP2C19*-Voriconazole education document. Alternative antifungal recommendations based on Moffitt's formulary and Infectious Disease recommendations.

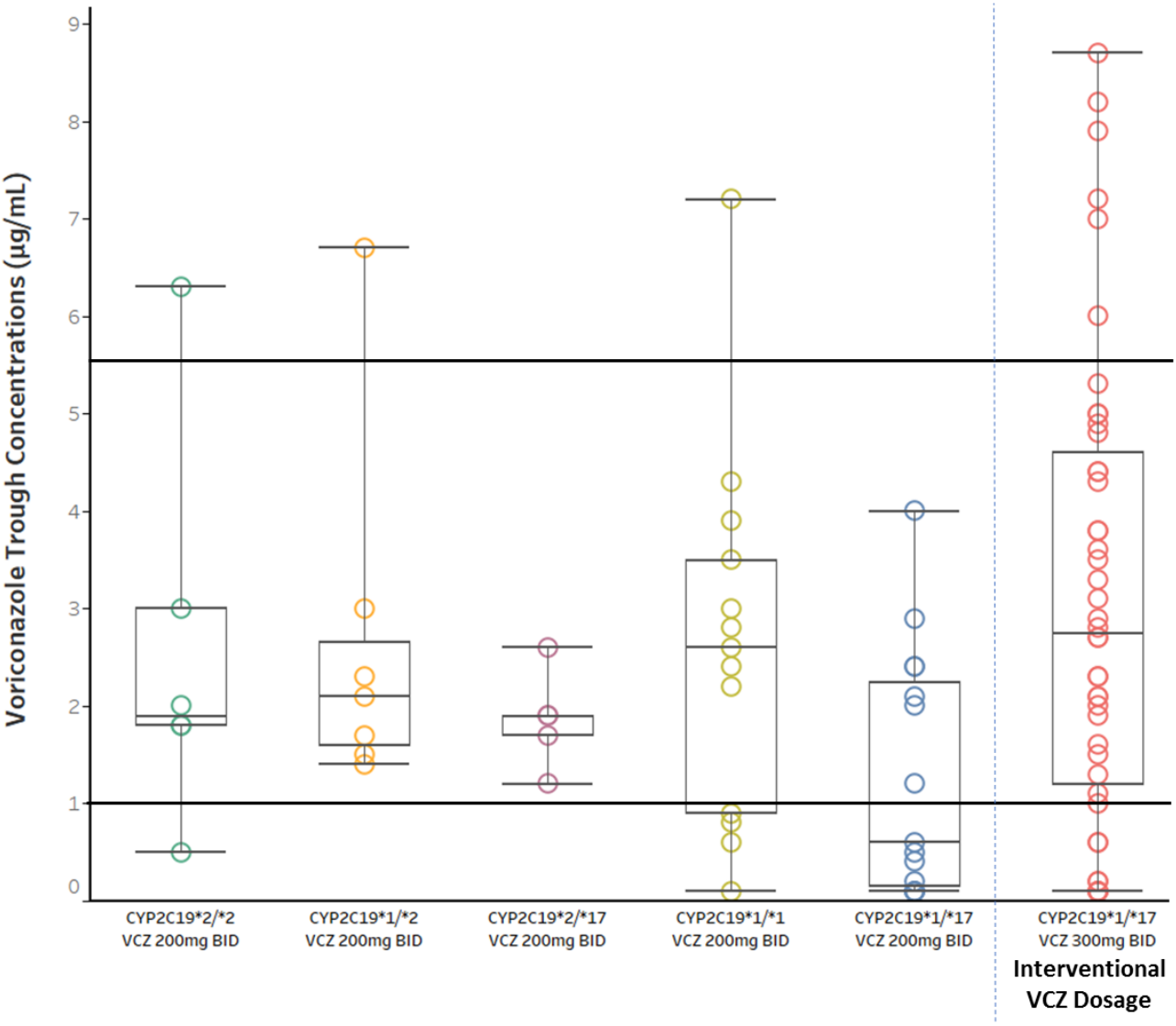


Figure S6. Voriconazole (VCZ) plasma trough concentrations were stratified by *CYP2C19* diplotype and dose. Total and median voriconazole trough concentrations are as follows: *CYP2C19*1/*17* receiving voriconazole 300 mg BID (n=44, median 2.7 µg/mL) or 200 mg BID (n=15, median 0.6 µg/mL); *CYP2C19*1/*1* (n=13, median 2.6 µg/mL), *CYP2C19*2/*17* (n=5, median 1.9 µg/mL), *CYP2C19*1/*2* (n=7, median 2.1 µg/mL), and *CYP2C19*2/*2* (n=6, median 1.9 µg/mL) receiving voriconazole 200 mg BID. The area between the solid black lines represents the goal trough concentration (1-5.5 µg/mL). The circles with a denser outline represent >1 trough concentration of the same value. To account for some patients having multiple voriconazole trough concentrations, statistical analysis was performed using a liner-mixed-effects model fitted to log-transformed voriconazole trough concentrations (Main Manuscript Figure 2). The box plot represents the median and interquartile range. BID = twice daily

Six unique patients who are CYP2C19 rapid metabolizers received voriconazole 300 mg twice daily and had troughs ranging from 6-8.7 µg/mL. One patient experienced neurotoxicity, one patient had an increase in liver enzymes, and 4 patients did not have a toxicity necessitating voriconazole discontinuation.

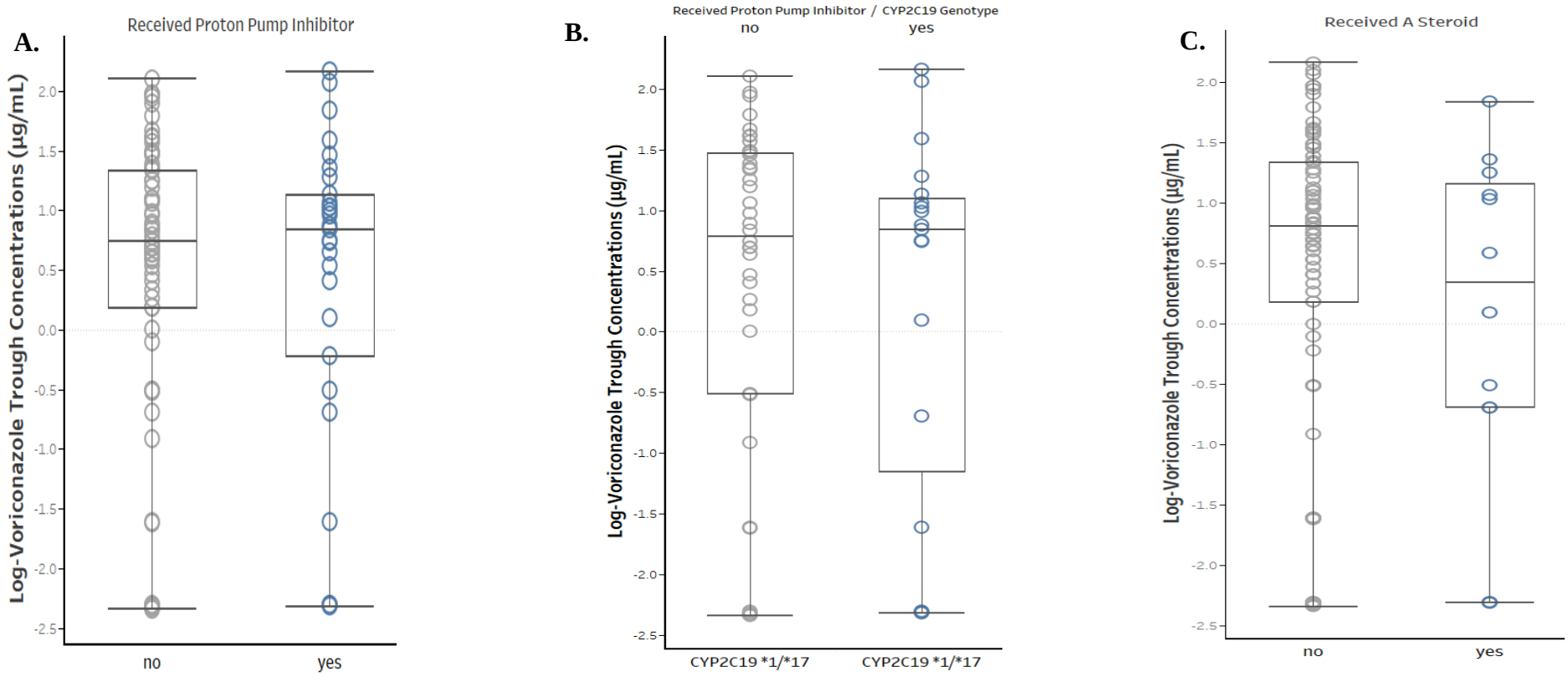


Figure S7: The influence of proton pump inhibitors and steroids on voriconazole plasma trough concentrations was investigated, as these drug classes are proposed to alter voriconazole metabolism. **A)** Voriconazole trough concentrations were similar between those who received a proton pump inhibitor (PPI) and those who did not receive a PPI (*P*=0.92). Of the 70 patients with voriconazole concentrations, 21 patients (30%) were concomitantly receiving a proton pump inhibitor (esomeprazole=1, omeprazole=4, pantoprazole=16). The most commonly prescribed PPI was pantoprazole, which is thought to have less influence on voriconazole concentrations when compared to other PPIs such as omeprazole. **B)** Voriconazole trough concentrations were similar among CYP2C19 rapid metabolizers who did or did not receive a PPI (*P*=0.74). **C)** Voriconazole trough concentrations were similar between those who did and did not receive a steroid (*P*=0.28). Seven patients (10%) were concomitantly receiving a steroid (dexamethasone=2, fludrocortisone=2, methylprednisolone=1, hydrocortisone=2). Five of the patients on steroids were also taking a PPI.