Supplementary Material for **Coupling Data Mining and Laboratory Experiments to Discover Drug Interactions Causing QT Prolongation**

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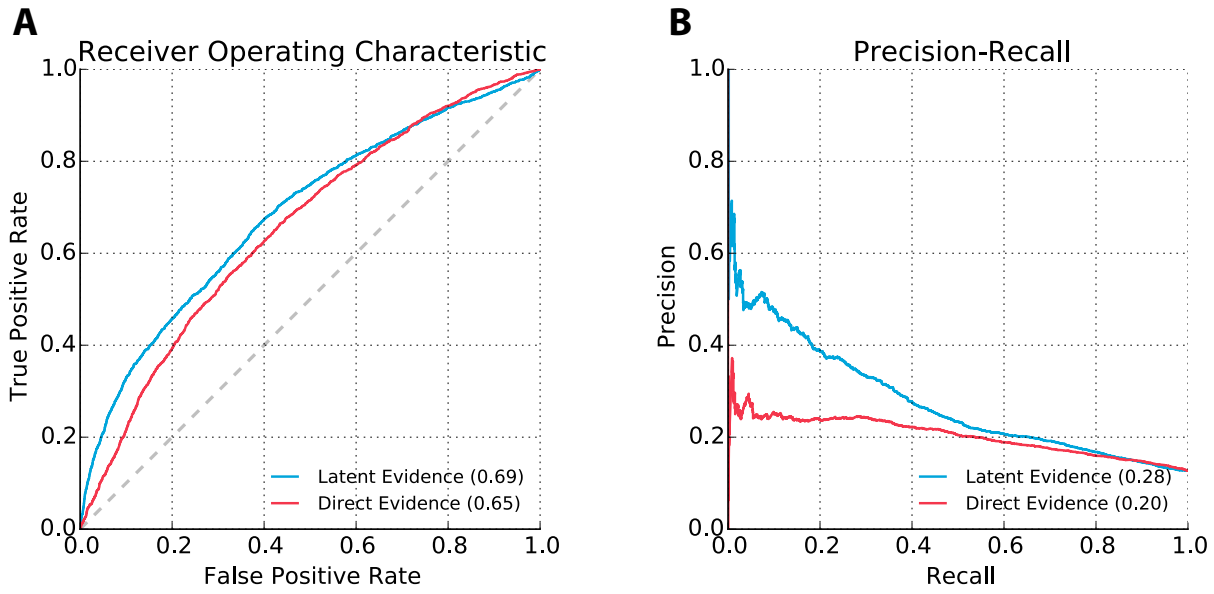
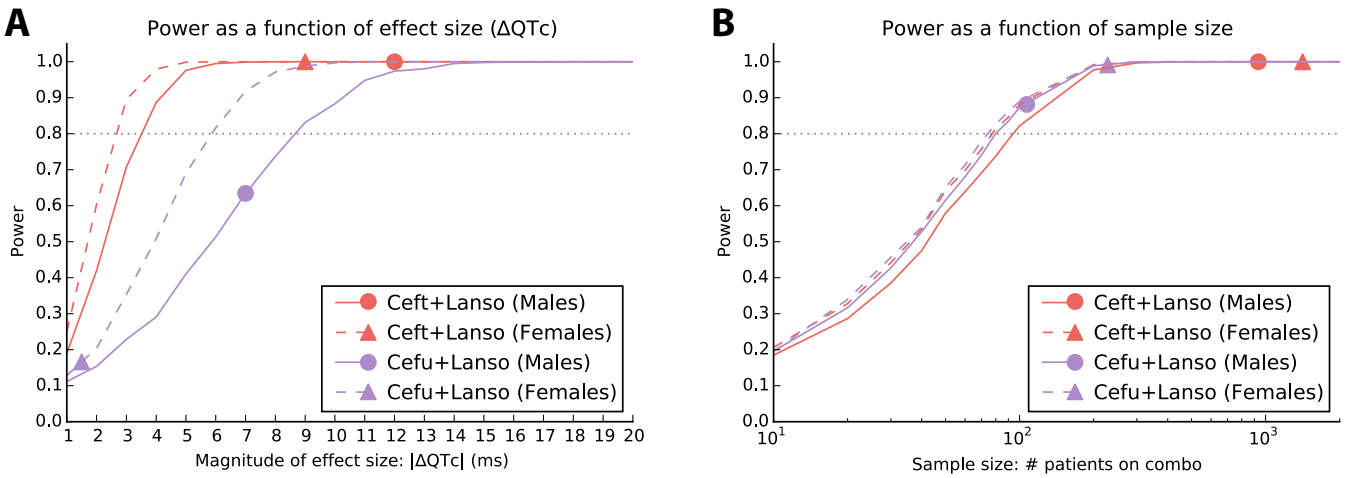


Supplementary Figure 1: Validation of latent signal detection side effect profile. In previous work we developed a profile consisting of 13 side effects in the FDA Adverse Event Reporting System (FAERS) that provide latent evidence of QT interval prolongation. Because no gold standard of QT-prolonging drug-drug interactions (QT-DDIs) exists, we validated the model by labeling all drug pairs in FAERS containing a known QT-prolonging drug (from CredibleMeds.org, see ref. 2 in main text) as a positive example. We compared the performance of this "latent" evidence model to a "direct" evidence model generated using the the six adverse events in the standardized MedDRA query for "Torsade de Pointes / QT prolongation". (**A**) Receiver operating characteristic (ROC) curve for both models. The area under the ROC curve indicated in parentheses. (**B**) Precision-recall curve for both models. The average precision is indicated in parentheses.



Supplementary Figure 2: Power analysis for retrospective QT-DDI corroboration in electronic health records. Because the distributions of QTc intervals were non-normal, we used the method of Collings and Hamilton to estimate the power of the Mann-Whitney U test to detect a change in QTc interval (see ref. 17 in main text). (**A**) Power as a function of the magnitude of effect size. For our predicted drug-drug interaction (ceftriaxone and lansoprazole, red) and our combination predicted not to interact (cefuroxime and lansoprazole, purple), we held the sample size constant (number of patients prescribed the combination) and estimated the statistical power to detect an effect size (change in QTc interval) between 1 and 20ms; the analysis was stratified by sex (males: solid lines; females: dashed lines). The dotted line represents the commonly used threshold for desired statistical power of 80%. For males (circles) and females (triangles), the marker indicates the effect size and corresponding power we observed for the given combination and sex in our EHR. (**B**) Power as a function of sample size. For ceftriaxone+lansoprazole and cefuroxime+lansoprazole, we held the effect size constant (10ms) and estimated the statistical power to detect that change in QTc interval while varying the sample size (number of patients prescribed the combination). Markers represent the number of patients prescribed each combination (stratified by sex) and the corresponding power; note that for both sexes prescribed both combinations we have sufficient statistical power to detect a 10ms change in QTc interval.

Supplementary Table 1: QT interval changes assessed using four heart rate correction formulae

Ceftriaxone + Lansoprazole

	Bazett			Fridericia			Framingham			Hodges		
Males	Ceft+Lanso	Ceft	Lanso	Ceft+Lanso	Ceft	Lanso	Ceft+Lanso	Ceft	Lanso	Ceft+Lanso	Ceft	Lanso
Median QTc (ms) [95% CI]	458.0 [398.0, 588.0]	446.0 [394.0, 566.0]	442.0 [395.0, 571.0]	430.5 [372.3, 557.0]	422.0 [364.0, 536.7]	425.0 [375.0, 548.0]	428.0 [374.3, 551.7]	420.0 [367.0, 527.0]	423.0 [377.0, 538.0]	434.0 [382.0, 554.7]	425.0 [379.0, 530.0]	426.0 [383.0, 541.0]
Patients with QTc ≥ 500ms (%)	19.27	14.21	12.41	9.85	7.73	7.53	8.24	5.91	6.62	8.99	6.38	7.01
ΔQTc (ms) [95% CI]	12.0 [7.0, 15.0]			5.5 [3.0, 8.5]			5.0 [1.5, 7.0]			8.0 [4.0, 10.0]		
P	3.09E-12			1.32E-04			2.65E-03			1.06E-07		
Females												
Median QTc (ms) [95% CI]	457.0 [401.0, 571.7]	448.0 [398.0, 560.0]	444.0 [399.0, 568.0]	429.0 [370.0, 544.7]	422.0 [366.0, 532.0]	427.0 [374.0, 542.0]	426.0 [372.3, 535.0]	420.0 [369.0, 521.0]	425.0 [376.0, 532.4]	432.0 [383.3, 537.0]	425.0 [381.0, 527.0]	428.0 [383.0, 536.0]
Patients with QTc ≥ 500ms (%)	16.34	11.43	11.61	8.56	5.4	6.45	6.72	4.39	5.47	7.85	4.98	5.96
ΔQTc (ms) [95% CI]	9.0 [5.2, 11.3]			2.0 [0.0, 5.0]			1.0 [-2.0, 3.0]			4.0 [0.5, 5.8]		
P	2.55E-13			0.012			0.129			7.09E-06		

Cefuroxime + Lansoprazole

	Bazett			Fridericia			Framingham			Hodges		
Males	Cefu+Lanso	Cefu	Lanso	Cefu+Lanso	Cefu	Lanso	Cefu+Lanso	Cefu	Lanso	Cefu+Lanso	Cefu	Lanso
Median QTc (ms) [95% CI]	450.0 [393.6, 579.4]	435.0 [391.9, 552.1]	443.0 [395.0, 572.0]	429.0 [368.6, 551.6]	416.5 [362.9, 525.2]	425.0 [375.0, 548.2]	427.0 [371.6, 538.5]	415.5 [366.0, 518.1]	424.0 [378.0, 538.0]	428.0 [379.6, 535.5]	418.5 [376.0, 526.0]	427.0 [383.0, 541.0]
Patients with QTc ≥ 500ms (%)	14.95	11.16	12.84	7.48	5.5	7.68	7.48	3.77	6.7	7.48	4.72	7.14
ΔQTc (ms) [95% CI]	7.0 [-4.5, 17.0]			4.0 [-13.1, 9.0]			3.0 [-10.0, 8.0]			1.0 [-8.6, 9.0]		
P	0.167			0.283			0.227			0.332		
Females												
Median QTc (ms) [95% CI]	443.5 [398.7, 579.2]	439.0 [397.0, 551.1]	445.0 [399.0, 569.0]	422.5 [366.0, 533.3]	416.0 [364.0, 514.1]	427.0 [373.8, 543.0]	422.0 [370.0, 520.5]	415.0 [366.0, 506.2]	426.0 [376.0, 534.0]	426.0 [380.4, 528.5]	418.0 [380.0, 513.1]	428.0 [383.0, 537.0]
Patients with QTc ≥ 500ms (%)	11.4	9.09	12.07	7.89	4.08	6.66	4.82	3.45	5.68	5.26	3.76	6.23
ΔQTc (ms) [95% CI]	-1.5 [-9.3, 4.3]			-4.5 [-8.8, 4.0]			-4.0 [-7.8, 0.8]			-2.0 [-7.0, 5.3]		
P	0.155			0.043			0.037			0.101		

Supplementary Table 2: Regression analysis confirming interaction effect between drug pair exposure and race.

Drug 1	Drug 2	Race	Intercept	DDI Exposure	Race	Sex	DDI Exposure × Race
Ceftriaxone	Lansoprazole	White	451.25 (450.52, 451.99) P<2e-16	8.01 (5.33, 10.71) P=3.937e-09	0.62 (-0.24, 1.49) P=0.158	-0.70 (-1.53, 0.14) P=0.104	**3.61** **(0.02, 7.23)** **P=0.049**
Ceftriaxone	Lansoprazole	Black	451.20 (450.59, 451.82) P<2e-16	9.92 (7.90, 11.96) P=3.805e-22	2.10 (0.94, 3.27) P=3.928e-04	-0.62 (-1.46, 0.22) P=0.145	0.18 (-4.29, 4.71) P=0.936
Ceftriaxone	Lansoprazole	Other	452.12 (451.47, 452.77) P<2e-16	11.34 (9.24, 13.46) P=1.249e-26	-1.86 (-2.81, -0.90) P=1.497e-04	-0.74 (-1.57, 0.10) P=8.513e-02	-5.49 (-9.57, -1.37) P=9.085e-03
Cefuroxime	Lansoprazole	White	450.71 (449.80, 451.62) P<2e-16	1.99 (-5.19, 9.29) P=0.589	0.33 (-0.70, 1.37) P=0.529	-0.96 (-1.98, 0.06) P=6.524e-02	-2.28 (-11.53, 7.17) P=0.634
Cefuroxime	Lansoprazole	Black	450.28 (449.53, 451.02) P<2e-16	1.16 (-3.81, 6.20) P=0.648	3.66 (2.24, 5.09) P=4.111e-07	-0.85 (-1.86, 0.17) P=0.103	-3.13 (-16.03, 10.15) P=0.640
Cefuroxime	Lansoprazole	Other	451.53 (450.75, 452.31) P<2e-16	0.04 (-5.23, 5.37) P=0.988	-2.38 (-3.56, -1.20) P=8.287e-05	-1.04 (-2.06, -0.01) P=4.683e-02	2.40 (-8.44, 13.50) P=0.668

We modeled the log(QTc) interval as a linear model of DDI exposure, sex, race, and the interaction of DDI exposure and race. Estimates above have been exponentiated back from the log scale and converted to units of milliseconds. Categorical variables: *Exposure* = 1 if exposed to drug pair, 0 otherwise. *Race* = 1 if patient is of the given race, 0 otherwise. *Sex* = 1 if patient is male, 0 if female. Each cell contains the coefficient estimate, 95% confidence interval, and p-value. We observed a significant positive interaction between exposure and race for whites (bolded).

Supplementary Table 3: Paired analysis of patients with ECG reports before and after combination therapy exposure. Numbers represent changes in the QTc (after exposure – before exposure).

Drug Pair	Sex	White	Black/African American	Other, including Hispanic
Ceftriaxone + Lansoprazole	M	14.0 ± 4.0 ms** (N=155)	1.5 ± 7.5 ms (N=51)	10.6 ± 6.8 ms (N=44)
Ceftriaxone + Lansoprazole	F	12.9 ± 3.3 ms** (N=198)	-8.3 ± 5.1 ms (N=82)	8.4 ± 4.9 ms (N=73)
Cefuroxime + Lansoprazole	M	22.1 ± 10.5 ms (N=15)	N/A	43.0 ± 15.3 ms (N=3)
Cefuroxime + Lansoprazole	F	-5.0 ± 6.8 ms (N=37)	1.7 ± 8.0 ms (N=7)	53.1 ± 27.0 ms (N=12)

† $P < 0.05$, one sample Student's T test

** $P < 0.01$