Using Real World Data to Fill Evidence Gaps for Precision Dosing

Sara Van Driest, MD, PhD
Assistant Professor of Pediatrics and Medicine
Disclosure

• I will present Real World Data extracted from electronic health records on drugs including statins, antibiotics, antipsychotics, and analgesics. Exposure data may include off-label use, by age or indication, for these drugs.

• I have received an honorarium as an invited speaker to Merck.
Objective

• Discuss examples of using clinically generated data to better understand drug-drug interactions, drug-gene interactions, and the clinical factors that influence drug response in specific populations.

• Appraise the utility and limitations to using clinically generated data to perform precision dosing research.
• Drug-Drug Interactions
  – Statin-daptomycin
  – Vancomycin-piperacillin/tazobactam
• Dose-Response
  – Statin
• Pharmacogenomics
  – Risperidone (adverse drug events)
  – Fentanyl (population PK)
Outline

• Drug-Drug Interactions
  – Statin-daptomycin
  – Vancomycin-piperacillin/tazobactam
• Dose-Response
  – Statin
• Pharmacogenomics
  – Risperidone (adverse drug events)
  – Fentanyl (population PK)

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Effect of Statin Coadministration on the Risk of Daptomycin-Associated Myopathy

Ryan K. Dare, Chad Tovell, Bryan Harris, Patty W. Wright, Sara L. Van Driest, Eric Farber-Eger, George E. Nelson, and Thomas R. Talbot

Background. Daptomycin-associated myopathy has been identified in 2%–14% of patients, and rhabdomyolysis is a known adverse effect. Although risk factors for daptomycin-associated myopathy are poorly defined, creatine phosphokinase (CPK) monitoring and temporary discontinuation of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or "statins," has been recommended.

Methods. We conducted a single-center, retrospective, matched case-control risk factor analysis in adult and pediatric patients from 2004 to 2015. Patients in whom myopathy (defined as CPK values above the upper limit of normal) developed during daptomycin treatment were matched 1:1 to no-myopathy controls with at least the same duration of therapy. Risk factors independently associated with myopathy were determined using multivariable conditional logistic regression. Secondary analysis was performed in patients with rhabdomyolysis, defined as CPK values ≥10 times the upper limit of normal.

Results. Of 3042 patients reviewed, 128 (4.2%) were identified as having daptomycin-associated myopathy, 25 (0.8%) of whom had rhabdomyolysis; 121 (95%) of the 128 were adults, and the mean duration of therapy before CPK elevation was 16.7 days (range, 1–58 days). In multivariate analysis, deep abscess treatment (odds ratio, 2.80; \( P = .03 \)), antihistamine coadministration (3.50; \( P = .03 \)), and statin coadministration (2.60; \( P = .03 \)) were independent risk factors for myopathy. Obesity (odds ratio, 3.28; \( P = .03 \)) and statin coadministration (4.67; \( P = .03 \)) were found to be independent risk factors for rhabdomyolysis, and older age was associated with reduced risk (0.97; \( P = .05 \)).

Conclusions. Statin coadministration with daptomycin was independently associated with myopathy and rhabdomyolysis. This is the first study to provide strong evidence supporting this association. During coadministration, we recommend twice-weekly CPK monitoring and consideration of withholding statins.

Keywords. daptomycin; myopathy; rhabdomyolysis; statin; drug-drug interaction.

Dare et al, Clin Infect Dis. 2018
Background

- **Daptomycin**
  - Used for *Staph, Strep, and Entercoccus* infections
  - Associated with myopathy (2-14%) and rhabdomyolysis (up to 5%)

- **Statin Drugs**
  - 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
  - Lipid lowering agents
  - Associated with myopathy (5-10%) and rhabdomyolysis (<0.1%)

https://dailymed.nlm.nih.gov/dailymed/, Daptomycin injection

Methods

- Retrospective (1990-2015) case control risk factor analysis
- Study cohort from Vanderbilt Synthetic Derivative
  - ≥72h of daptomycin exposure
  - Normal CPK at initiation of therapy
  - No surgery in first 7 days of therapy
- Cases:
  - CPK >200 U/L during therapy
  - No alternate causes of CPK elevation on manual review
- Controls:
  - At least 1x normal CPK during therapy
  - Matched 1:1 for duration of therapy

Dare et al, Clin Infect Dis. 2018
Synthetic Derivative

Electronic Health Records Data
- Notes
- Lab Results
- Drug Exposure
- Billing Codes

De-Identification

Synthetic Derivative
>2.5 million individuals
## Demographics and Comorbid Conditions of Cases and Matched Controls

Dare et al, *Clin Infect Dis.* 2018

<table>
<thead>
<tr>
<th>Characteristic or Condition</th>
<th>Controls (n = 128)</th>
<th>Case Patients (n = 128)</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>53.2 (18.2)</td>
<td>48.2 (17.1)</td>
<td>0.99</td>
<td>.04b</td>
</tr>
<tr>
<td>Female sex</td>
<td>50 (39)</td>
<td>57 (45)</td>
<td>1.30</td>
<td>.35</td>
</tr>
<tr>
<td>White race</td>
<td>106 (83)</td>
<td>98 (77)</td>
<td>0.97</td>
<td>.82</td>
</tr>
<tr>
<td>BMI $&gt;$30 kg/m$^2$</td>
<td>45 (35)</td>
<td>61 (48)</td>
<td>1.84</td>
<td>.03b</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>13 (10)</td>
<td>17 (13)</td>
<td>1.36</td>
<td>.44</td>
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<tr>
<td>Cirrhosis</td>
<td>8 (6)</td>
<td>1 (1)</td>
<td>0.13</td>
<td>.05b</td>
</tr>
<tr>
<td>CKD</td>
<td>21 (16)</td>
<td>22 (17)</td>
<td>1.06</td>
<td>.87</td>
</tr>
<tr>
<td>Dialysis</td>
<td>17 (13)</td>
<td>8 (6)</td>
<td>0.40</td>
<td>.06b</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (9)</td>
<td>14 (11)</td>
<td>1.33</td>
<td>.51</td>
</tr>
<tr>
<td>DM</td>
<td>38 (30)</td>
<td>44 (34)</td>
<td>1.26</td>
<td>.41</td>
</tr>
<tr>
<td>HIV infection</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0.33</td>
<td>.34</td>
</tr>
<tr>
<td>Cancer</td>
<td>33 (26)</td>
<td>22 (17)</td>
<td>0.58</td>
<td>.09b</td>
</tr>
<tr>
<td>BMT</td>
<td>9 (7.0)</td>
<td>11 (9)</td>
<td>1.22</td>
<td>.66</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>14 (11)</td>
<td>14 (11)</td>
<td>1.00</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>4 (3)</td>
<td>8 (6)</td>
<td>2.00</td>
<td>.60</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>33 (26)</td>
<td>25 (20)</td>
<td>0.67</td>
<td>.21</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>11 (9)</td>
<td>3 (2)</td>
<td>0.20</td>
<td>.04b</td>
</tr>
</tbody>
</table>

*Data represent No. (%) of patients unless otherwise specified.

*Significant at $P < .10$. 

Dare et al, *Clin Infect Dis.* 2018
## Results of Multivariable Analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>.16</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>1.48</td>
<td>.25</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.16</td>
<td>.10</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.39</td>
<td>.14</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.55</td>
<td>.16</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.28</td>
<td>.53</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1.74</td>
<td>.11</td>
</tr>
<tr>
<td>Deep abscess</td>
<td>2.80</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Antihistamine coadministration</strong></td>
<td>3.50</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Statin coadministration</strong></td>
<td>2.60</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; OR, odds ratio.

*aSignificant at P ≤ .05.
• In this dataset, statin coadministration is associated with increased risk of myopathy
• **Discontinue statins while on daptomycin**
• Assure compliance with CPK monitoring
• Consider twice weekly CPK and Creatinine monitoring in high risk patients

• **LIMITATIONS**: Retrospective (ascertainment bias, no causality, data limited to clinical documentation); Small sample size; Single center.

Dare et al, *Clin Infect Dis*. 2018
Outline

• Drug-Drug Interactions
  – Statin-daptomycin
  – Vancomycin-piperacillin/tazobactam

• Dose-Response
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• Pharmacogenomics
  – Risperidone (adverse drug events)
  – Fentanyl (population PK)

Cook et al, J Pediatric Infect Dis Soc. 2018

Incidence of Nephrotoxicity Among Pediatric Patients Receiving Vancomycin With Either Piperacillin–Tazobactam or Ceftazidime: A Cohort Study

Kathryn M. Cook, Jessica Gillon, Alison G. Griswold, Rita Bamerjian, Natalie Jimenez-Trujillo, Elizabeth J. Phillips, and Sara L. Van Driest

Department of Pharmaceutical Services, Pediatrics, and Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Background. Recent studies in adults have found an incidence of acute kidney injury (AKI) in patients treated with a combination of vancomycin and piperacillin–tazobactam (TZP) that is greater than that expected with either medication alone. The purpose of this study was to determine whether combination therapy with vancomycin and TZP is associated with an incidence of AKI in pediatric patients higher than that in those on combination therapy with vancomycin and cefepime.

Methods. We performed a retrospective single-center matched-cohort study of pediatric patients who received vancomycin in combination with TZP or cefepime between January 2015 and June 2016. The patients were matched according to chronic disease, age, sex, and number of concomitant nephrotoxic medications at the time of combination antibiotic therapy. The primary outcome was incidence of AKI. Secondary outcomes included differences between groups in time to AKI, resolution of AKI, and effect of vancomycin trough levels on the incidence of nephrotoxicity. Conditional logistic regression was used to compare categorical and continuous variables between treatment groups. Conditional Poisson regression was used to assess the association between AKI and treatment groups. Stratified log-rank tests and Cox proportional hazards models with shared frailty were used to compare the times to AKI according to treatment group.

Results. Two hundred twenty-eight matched patients were included. AKI developed in 9 (7.9%) of 114 and 33 (28.9%) of 114 patients in the cefepime and TZP groups, respectively (P < .001). Type of combination therapy remained a significant predictor for AKI in multivariate conditional Poisson analysis in which adjustments were made for age, sex, use of concomitant nephrotoxicants, and vancomycin dose (relative risk, 2.5 [95% confidence interval, 1.1–5.8]; P = .03). AKI developed almost 3 times sooner in the TZP group than in the cefepime group (hazard ratio, 2.9 [95% confidence interval, 1.3–6.1]; P = .006). Sensitivity analyses in which adjustment was made for antibiotic indication in addition to the aforementioned variables and excluding those with gastrointestinal infection revealed similar results.

Conclusion. Among hospitalized children at our institution, combination therapy with vancomycin and TZP was associated with an incidence of AKI higher than that associated with vancomycin and cefepime.

Keywords. acute kidney injury; nephrotoxicity; pediatrics; tazobactam–piperacillin; vancomycin.
Background and Methods

Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children

Kevin J. Downes, MD; Carter Cowden, MPH; Benjamin L. Laskin, MD, MS; Yuan-Shung Huang, MS; Wu Gong, MS, MPH; Matthew Bryan, PhD; Brian T. Fisher, DO, MPH, MSCE; Stuart L. Goldstein, MD; Theoklis E. Zaoutis, MD, MSCE

**IMPORANCE** β-Lactam antibiotics are often coadministered with intravenous (IV) vancomycin hydrochloride for children with suspected serious infections. For adults, the combination of IV vancomycin plus piperacillin sodium/tazobactam sodium is associated with a higher risk of acute kidney injury (AKI) compared with vancomycin plus 1 other β-lactam antibiotic. However, few studies have evaluated the safety of this combination for children.

**OBJECTIVE** To assess the risk of AKI in children during concomitant therapy with vancomycin and 1 antipseudomonal β-lactam antibiotic throughout the first week of hospitalization.

![Timeline of Cefepime Restricted Periods](timeline.png)

- **6/15/2015 - 8/6/2015**: Cefepime Restricted
- **5/12/2016 - 6/30/2016**: Cefepime Restricted

Downes et al, *JAMA Pediatrics*. 2017
Cook et al, *J Pediatric Infect Dis Soc*. 2018
Results and Recommendations

Univariate Analysis of AKI in 228 Matched Children

- Vancomycin + Cefepime (N=114): 8%
- Vancomycin + TZP (N=114): 29%

p<0.001

Adjusted Analysis of AKI in 228 Matched Children

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Odds Ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin + Cefepime</td>
<td>Reference</td>
<td>2.5 [1.1-5.8]</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, nephrotoxins, and vancomycin dose

- Monitor
- De-escalate
- Drug shortages affect patients

Cook et al, J Pediatric Infect Dis Soc. 2018
Outline

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  – Statin-daptomycin
  – Vancomycin-piperacillin
• Dose-Response
  – Statin
• Pharmacogenomics
  – Risperidone (adverse drug events)
  – Fentanyl (population PK)

Characterization of Statin Dose Response in Electronic Medical Records

W-Q Wei, Q Feng, L Jiang, MS Waitara, OF Iwuchukwu, DM Roden, M Jiang, H Xu, RM Krauss, JI Rotter, DA Nickerson, RL Davis, RL Berg, PL Peissig, CA McCarty, RA Wilke, and JC Denny

Efforts to define the genetic architecture underlying variable statin response have met with limited success, possibly because previous studies were limited to effect based on a single dose. We leveraged electronic medical records (EMRs) to extract potency ($ED_{50}$) and efficacy ($E_{max}$) of statin dose–response curves and tested them for association with 144 preselected variants. Two large biobanks were used to construct dose–response curves for 2,026 and 2,252 subjects on simvastatin and atorvastatin, respectively. Atorvastatin was more efficacious, was more potent, and demonstrated less interindividual variability than simvastatin. A pharmacodynamic variant emerging from randomized trials (PRDM16) was associated with $E_{max}$ for both. For atorvastatin, $E_{max}$ was 51.7 mg/dl in subjects homozygous for the minor allele vs. 75.0 mg/dl for those homozygous for the major allele. We also identified several loci associated with $ED_{50}$. The extraction of rigorously defined traits from EMRs for pharmacogenetic studies represents a promising approach to further understand the genetic factors contributing to drug response.

Wei et al, Clin Pharm Ther. 2014
Background and Methods

• Simvastatin and atorvastatin
  – Commonly used lipid-lowering drugs
  – RCTs identified potential pharmacogenomic associations

• Use longitudinal EHR data
  – Individuals with multiple dosing regimens
  – Serial lipid measurements
  – Candidate genetic variants

\[
\text{LDL}_{\text{Dose}} = E_0 - \frac{E_{\text{max}} \times \text{Dose}}{\text{ED}_{50} + \text{Dose}}
\]

Wei et al, Clin Pharm Ther. 2014
The BioVU Resource

Electronic Health Records Data
- Notes
- Lab Results
- Drug Exposure
- Billing Codes

De-Identification

DNA from Discarded Blood Samples

Synthetic Derivative
- >2.5 million individuals

BioVU
- >240,000 DNA samples
- >30,000 pediatric
Results

Simvastatin

Atorvastatin
## Results

Variants associated with response to SIMVASTATIN

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect Size (Efficacy)</th>
<th>P Value</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M/M</td>
<td>M/m</td>
<td>m/m</td>
</tr>
<tr>
<td>rs6588480</td>
<td>61.86±24.38</td>
<td>57.40±21.14</td>
<td>59.46±17.88</td>
</tr>
<tr>
<td>rs776746</td>
<td>61.22±23.72</td>
<td>60.06±22.21</td>
<td>55.71±21.70</td>
</tr>
<tr>
<td>rs7564379</td>
<td>61.00±23.44</td>
<td>59.92±22.07</td>
<td>56.53±27.90</td>
</tr>
<tr>
<td>rs17091962</td>
<td>59.97±23.01</td>
<td>64.01±25.09</td>
<td>66.51±22.13</td>
</tr>
<tr>
<td>rs1800961</td>
<td>60.16±23.26</td>
<td>66.71±23.62</td>
<td>58.76±26.03</td>
</tr>
<tr>
<td>rs2740574</td>
<td>61.07±23.65</td>
<td>58.87±20.73</td>
<td>57.12±23.93</td>
</tr>
<tr>
<td>rs11807862</td>
<td><strong>60.92±23.34</strong></td>
<td><strong>59.50±23.02</strong></td>
<td><strong>53.23±23.51</strong></td>
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</table>

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect Size (Potency)</th>
<th>P Value</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M/M</td>
<td>M/m</td>
<td>m/m</td>
</tr>
<tr>
<td>rs1555926</td>
<td>7.63±3.27</td>
<td>7.00±2.82</td>
<td>7.08±2.86</td>
</tr>
<tr>
<td>rs17645290</td>
<td>7.33±2.99</td>
<td>7.57±3.47</td>
<td>8.53±3.63</td>
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<td>7.40±2.95</td>
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<td>rs4438302</td>
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<td>7.41±3.18</td>
<td>7.88±3.61</td>
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<tr>
<td>rs6029526</td>
<td>7.54±3.40</td>
<td>7.53±2.97</td>
<td>7.10±3.10</td>
</tr>
</tbody>
</table>

M/M = homozygous major allele, M/m = heterozygous, m/m = homozygous minor allele

Wei et al, *Clin Pharm Ther*. 2014
• Atorvastatin is more efficacious, more potent, less individual variability than simvastatin

• Identified drug-gene interactions: Patients genetically predisposed to low potency of simvastatin may need a more potent statin

• **LIMITATIONS**: Selection bias; No replication of genetic findings; Compliance unknown
Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin/tazobactam
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse drug events)
  - Fentanyl (population PK)

References:

Oshikoya et al, *Peds Res.* 2019
Background: Few pediatric patients undergo PGx testing
Background: Lack of evidence for pediatric PGx

<table>
<thead>
<tr>
<th>Annual Pediatric Drug Exposures</th>
<th>Number of Manuscripts</th>
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<tr>
<td>&gt; 500</td>
<td>10</td>
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<tr>
<td>100-500</td>
<td>13</td>
</tr>
<tr>
<td>50-100</td>
<td>3</td>
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<tr>
<td>10-50</td>
<td>5</td>
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<tr>
<td>&lt; 10</td>
<td>10</td>
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</table>

Results from BioVU Cohort

Cohort Summary Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>8.3 (6.3-10.5)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>188 (73%)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>76 (30%)</td>
</tr>
<tr>
<td>Metabolizer Status</td>
<td></td>
</tr>
<tr>
<td>Ultrarapid</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Normal</td>
<td>218 (85%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Poor</td>
<td>15 (6%)</td>
</tr>
</tbody>
</table>

Number (%) or Median (Interquartile Range)

Univariate Analysis of Adverse Drug Events in 251 Children

<table>
<thead>
<tr>
<th>CYP2D6 Metabolizer Status</th>
<th>Poor or Intermediate (n=33)</th>
<th>Normal (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45</td>
<td>27</td>
</tr>
</tbody>
</table>

p=0.04

Oshikoya et al. Pediatric Res 2019
Common Theme in Pharmacogenetics

Dose  \[\text{PGx Influence}\]  Response

- Drug Disposition
- Biological Effect
- Concentration
- PGx Influence
Clinical Sources for Pop PK Dataset

- Pediatric cardiac surgery patients
- Fentanyl doses from EHR
- All covariates from EHR
- All remnant plasma from chemistry lab scavenged for fentanyl concentration measurement

Van Driest et al, Br J Clin Pharm. 2016
PopPK Model – Pharmacogenetic analyses in progress!

Van Driest et al, Br J Clin Pharm. 2016
Final Summary

• EHR data can be used to define a wide variety of drug related traits

• Variability inherent to “routine” clinical care creates natural experiments

• Inherent limitations to retrospective data collection and “real world” data
Acknowledgements

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• Brian Hachey

Statin Daptomycin
• Ryan Dare
• Chad Tewell
• Bryan Harris
• Patty Wright
• Eric Farber-Eger
• George Nelson
• Thomas Talbot

AKI and TZP
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• Jessica Gillon
• Alison Grisso
• Ritu Banerjee
• Natalia Jimenez-Truque
• Elizabeth J. Phillips

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• Quiping Feng
• Lan Jiang
• Otito Iwuchukwu
• Dan Roden
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