PERSPECTIVES ON RESEARCH FROM A DIALYSIS PROVIDER

Franklin W. Maddux, MD FACP
Fresenius Medical Care

September 9, 2016
Paris, France
Disclosure of Interests

Franklin W. Maddux, MD FACP
Executive Vice President for Clinical & Scientific Affairs
Chief Medical Officer
Fresenius Medical Care North America

Disclosure:
Fresenius Medical Care
Employment
Stock Ownership
The Next 30 Minutes
A Perspective from Fresenius Medical Care

Where Are Insights Found?
Observational Data and Research
Intersection of Analytics and Clinical Research
Research Collaborations
Addressing Pragmatic Questions
Prospective National Trials

KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology
September 8-11, 2016 | Paris, France
The Fresenius Group

FRESENIUS SE

FRESENIUS MEDICAL CARE 31%

100%

FRESENIUS KABI

100%

FRESENIUS HELIOS

77%

FRESENIUS VAMED

Fresenius SE Business Segments

Overview

- World’s leading provider of services and products for High Cost Acute and Chronic Episodes of Care
- Renal Disease Care, Hospitalist Services, Cardiology, Vascular Disease

FRESENIUS MEDICAL CARE

- Offers infusion therapies, intravenously administered drugs and clinical nutrition
- Transfusion & blood processing technologies

FRESENIUS KABI

- One of largest private hospital operators in Germany
- 155 hospitals in Germany & Spain

FRESENIUS HELIOS

FRESENIUS VAMED

- Engineering and Services for Hospitals and other Health Care facilities
Fresenius Medical Care
Dialysis Related Footprint

301,548 PATIENTS SERVED
45 M TREATMENTS
3,504 CLINICS

37 PRODUCTION SITES
106,556 EMPLOYEES
<table>
<thead>
<tr>
<th>Fresenius Medical Care North America</th>
<th>Assets Generating Data for Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresenius Kidney Care</td>
<td>Dialysis Services</td>
</tr>
<tr>
<td>Sound Physicians</td>
<td>Acute Episodes of Care</td>
</tr>
<tr>
<td>Fresenius Vascular Care</td>
<td>Interventional Radiology</td>
</tr>
<tr>
<td>Fresenius Rx</td>
<td>Pharmacy</td>
</tr>
<tr>
<td>Spectra Laboratories</td>
<td>Laboratory</td>
</tr>
<tr>
<td>National Cardiovascular Partners</td>
<td>Cardiology</td>
</tr>
<tr>
<td>Pacific Cardiology Associates</td>
<td>Cardiology</td>
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<tr>
<td>Acumen Physician Solutions</td>
<td>Health IT Services</td>
</tr>
<tr>
<td>Fresenius Physician Practice Services</td>
<td>Practice Management</td>
</tr>
<tr>
<td>MedSpring Urgent Care</td>
<td>Urgent Care Practices</td>
</tr>
<tr>
<td>Fresenius Health Partners</td>
<td>Health Insurance</td>
</tr>
<tr>
<td>Frenova Renal Research</td>
<td>Clinical Research</td>
</tr>
<tr>
<td>Fresenius Renal Therapies</td>
<td>Devices and Pharma</td>
</tr>
<tr>
<td>Renal Research Institute</td>
<td>Biological Research</td>
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</table>

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Categories of Clinical Research Efforts

- Observational Research Protocols
- Prospective Public Research
- Master Collaborative Research with Institutions
- Pharma or Industry Sponsored Clinical Trials
- Analytical Insights Research
- Clinical Comparative Effectiveness
- Concurrent Operational Observational Analysis
- Investigator Initiated Studies
- Licensing De-identified Data for Research
- Predictive Analytics & Modeling
- Physiologic Modeling Research
- Publication and Presentation
Heritability of Risk for Sudden Cardiac Arrest in ESRD

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*Nephrology Division, ‡Center for Human Genetic Research, Cardiovascular Research Center, and §Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts; and †Clinical Research Division, Fresenius Medical Care North America, Waltham, Massachusetts

ABSTRACT
Patients on dialysis are 20 times more likely to have a cardiac arrest compared with the general population. We considered whether inherited factors associate with cardiac arrest among patients on dialysis. From a sample of 647,457 patients on chronic dialysis, we identified 5117 pairs of patients who came from the same family. These patients were each matched to a control subject from the same population. McNemar’s tests were used to compare the risk of cardiac arrest between the familial related and unrelated pairs. Genetically related family members who did not cohabitate had an odds ratio of 1.88 (95% confidence interval [95% CI], 1.25 to 2.84) for cardiac arrest compared with their phenotypically matched unrelated controls. Genetically related family members who lived together in the same environment had an odds ratio of 1.66 (95% CI, 1.20 to 2.28). Spouses, who are genetically unrelated but live together in the same environment, had an odds ratio of 0.95 (95% CI, 0.60 to 1.59) for cardiac arrest. The risk of cardiac arrest in patients on dialysis may be attributable to inherited factors. Additional studies are needed to identify such candidate genes that modify cardiovascular risk in ESRD.

Figure 1. Higher prevalence of intrafamily cardiac arrest (patients) compared with matched unrelated pairs (controls). Family pairs: parent/child (n=1695), siblings (n=1602), cousin/uncle (n=756), or spouses (n=1064).
>1.2 million ESRD patients
>300 million dialysis treatments
>1.2 billion medications administered
>1.3 billion lab results
Observational Research Protocols
FMCNA CKD Registry Data Warehouse

>800,000 Staged CKD-ND patients
>20 million provider encounters
>16 million medications noted
>150 million lab results
Observational Research Protocols
MONDO Initiative

- MONDO (MONitoring Dialysis Outcomes) initiative was formed in the summer of 2010

- It’s based on existing relationship with University of Maastricht, FMC Asia Pacific, FMC Canada, Kuratorium für Heimdialyse (KfH) Germany

And new collaboration with FMC EMELA, Imperial College, Hadassah Medical Center, Pontifical Catholic University of Parana
• Pontifical Catholic University of Parana, Brazil
• Imperial College, UK
• University of Maastricht, The Netherlands
• Hadassah Medical Center, Israel
• Kuratorium für Dialyse und Nierentransplantation (KfH), Germany
• Nephro-Solutions Group, Germany
• Catharina Hospital, Eindhoven, The Netherlands
• Khartoum University Hospital, Sudan
• Renal Research Institute, USA
• FMC Europe, Middle East, Latin America
• FMC Asia Pacific
• FMC Canada
• FMC Mexico
Observational Research Protocols
MONDO Data

• Time range: 2000 to 2014 (data is updated annually)
• Number of clinics: ~1,500
• Number of patients: ~200,000
• Number of treatment and laboratory records: ~60,000,000
• Where:
  – six continents
  – 41 countries
<table>
<thead>
<tr>
<th>Observational Research Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries Represented in MONDO</td>
</tr>
</tbody>
</table>

- **Asia/Australia**
  - Australia
  - China (Hong Kong)
  - Malaysia
  - New Zealand
  - Philippines
  - Singapore
  - South Korea
  - China (Taiwan)
  - Thailand

- **North America**
  - Canada
  - USA

- **South America**
  - Argentina
  - Brazil
  - Chile
  - Colombia
  - Venezuela

- **Africa**
  - South Africa

- **Europe/Middle East**
  - Bosnia
  - Czech Republic
  - Croatia
  - Estonia
  - France
  - Germany
  - Hungary
  - Ireland
  - Bosnia
  - Czech Republic
  - Croatia
  - Estonia
  - France
  - Germany
  - Hungary
  - Ireland

  - **Europe/Middle East**
    - Bosnia
    - Czech Republic
    - Croatia
    - Estonia
    - France
    - Germany
    - Hungary
    - Ireland
    - Israel
    - Italy
    - Netherlands
    - Portugal
    - Poland
    - Romania
    - Russia
    - Slovenia
    - Slovakia
    - Spain
    - Serbia
    - Sweden
    - Turkey
    - UAE
    - Ukraine
    - UK
**Table 2. TiME Trial design**

<table>
<thead>
<tr>
<th>Design Element</th>
<th>Details</th>
</tr>
</thead>
</table>
| Treatment groups     | Intervention: dialysis facility adopts approach of prescribing hemodialysis session duration of ≥4.25 h  
                       | Usual Care: no trial-driven approach to hemodialysis session duration                                                                   |
| Randomization        | Cluster-randomization by dialysis facility  
                       | Stratification by provider organization, facility race distribution, and facility catheter use                                          |
| Target sample size   | 6432 patients  
                       | 402 clusters                                                                                                                             |
| Eligibility criteria – patients | Age ≥18 yr  
                       | Initiation of maintenance hemodialysis within the past 120 d  
                       | Ability to provide consent for dialysis  
                       | Currently treated with in-center hemodialysis                                                                 |
| Eligibility criteria – facilities | Agreement by facility leadership and nephrologists to adopt trial intervention  
                       | Capacity to accommodate treatment session durations of ≥4.25 h for incident patients                                                       |
Master Collaborative Research with Academic Institutions

Provides a framework for academic institutions and FMCNA to collaborate in data-driven research and clinical care innovation.

Facilitates and encourages collaboration across areas of mutual clinical interest.

Provides opportunity for active involvement of researchers, professionals, and fellows between the two entities.

Serves as an efficient mechanism for FMCNA to consider and evaluate investigator-initiated projects (especially those of nephrology faculty & fellows).

Enables the use of de-identified data corrals and bio-specimens in research, with the legal protections and collaboration arrangement understood and in place for all projects between FMCNA and the academic institution.
Master Collaborative Research with Academic Institutions

Structure of the Agreement

Overall legal obligations and responsibilities are set forth in the Master Collaborative Research agreement.

Each project is then presented as a Research Concept Proposal.

When approved, the specific project is then described in a Statement of Work, which outlines the precise data or bio specimens being licensed under the master agreement and, each parties’ specific responsibilities to the specific project.

The research is designed to be more than a data license, but a full collaborative research project between the academic institution researchers and FMCNA researchers.
Pharma or Industry Sponsored Clinical Trials
Frenova Renal Research

Renal disease type

21% Pre-dialysis  79% Dialysis

Disciplines
- Anemia
- Bone and mineral metabolism
- Biosimilars
- Vascular access
- Cardio-renal investigations
- Dialysis-dependent care
- Non-dialysis dependent CKD
Analytical Insights Research

Value Based Payment System Example

**MEDICARE COSTS THROUGH TRANSITION TO RENAL REPLACEMENT THERAPY**

PPPMP expenditures ($, in 1,000s)

- $15
- $12
- $9
- $6
- $3

Late Stage CKD

Incident ESRD

Prevalent ESRD

Months Pre- & Post- Initiation

-6 -5 -4 -3 -2 -1 1 2 3 4 5 6
### FMC Correlation Coefficients

1. Personal Care & Attention  | 0.728  
2. Anticipate Needs        | 0.721  
3. Respect & Dignity       | 0.708  
4. Hope                    | 0.705  
5. Quality of Clinical Care| 0.692  
6. Resolve Issues          | 0.688  
7. Team Members That Help  | 0.680  
8. Loved Ones Feel Welcome | 0.670  

*The Human Element*
Physiologic Modeling Research
Example: Anemia

Erythropoiesis cell lineage
Physiologic Modeling Research
Mathematical Modeling of the Anemia Patient Physiology

**Anemia Algorithms**

- **V5**
  - Current cMAB computerized algorithm
  - 65000 patients

- **B**
  - Pilot with Basal EPO on hold, 25% reduction
  - 4630 patients

- **C**
  - Pilot with basal EPO on hold, 50% reduction
  - 3213 patients

- **A**
  - Alternate CMAB A – like Arizona
  - 5700 patients

- **Other**
  - Hawaii, Kaiser, other individual algorithms, residual V4 (<15,000)
  - 52000 patients

Dustin Kapraun, Peter Kotanko, Franz Kappel and Doris Furtinger
Clinical Comparative Effectiveness

\[ V = \frac{Q + S}{\$} \]

(QUALITY)  (SERVICE)  (COST)
Clinical Comparative Effectiveness
The Four Quad Plot

FMCNA anemia management value proposition chart for ESA

Quadrant 4
Higher cost
Lower quality

Quadrant 2
Higher cost
Higher quality

Quadrant 3
Lower cost
Lower quality

Quadrant 1
Lower cost
Higher quality

$50
$25

15%
50%

Concurrent Observational Analysis
Hemoglobin Performance

HGB 3 Month and 1 Month Outcome

<table>
<thead>
<tr>
<th>Mircera</th>
<th>Aranesp</th>
<th>EPO IV</th>
<th>EPO SC</th>
<th>No ESA</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>21%</td>
<td>49%</td>
<td>19%</td>
<td>27%</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td>16%</td>
<td>54%</td>
<td>15%</td>
<td>13%</td>
<td>46%</td>
<td>44%</td>
</tr>
<tr>
<td>9%</td>
<td>9%</td>
<td>4%</td>
<td>10%</td>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>10%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>1%</td>
<td>3%</td>
<td>8%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

HGB Lab Percent

HGB Lab Results

69%

66%

10-12 g/dL

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Investigator Initiated Studies

Frenova’s support of research in non-industry-sponsored trials

- Investigator initiated
- Academic and other funding sources
- Large, publicly funded

<table>
<thead>
<tr>
<th>Year</th>
<th>Investigator Initiated</th>
<th>Academic and Other Funding Sources</th>
<th>Large, Publicly Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of trials

Source: 2015 FMCNA data

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Licensing De-identified Data for Research

Studying Transition of Care Costs

Results

The characteristics of the four cohorts defined for this study are described in Table 1. Each cohort includes between 14,000 and 31,000 patients. Close to half or more of the patients in each cohort are between the ages of 55 and 64. Patients are approximately twice as likely to have coverage through their own employment compared with a spouse’s employment. While there is cohort representation for each of the four major geographic regions, there is greater representation of Americans living in the South. The average length of follow-up used to examine costs for each cohort ranged from 3.0 months for the incident chronic dialysis cohort to 12.4 months for the prevalent chronic dialysis cohort.

Table 1: Cohort Demographics

<table>
<thead>
<tr>
<th></th>
<th>CKD Stage 4</th>
<th>CKD Stage 5</th>
<th>ESRD Incident</th>
<th>ESRD Prevalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>31,540</td>
<td>14,245</td>
<td>14,215</td>
<td>22,926</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>18.5</td>
<td>7.5</td>
<td>3.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Age* (Mean(SD))</td>
<td>54.0 (9.3)</td>
<td>52.2 (10.0)</td>
<td>50.5 (11.0)</td>
<td>52.0 (10.2)</td>
</tr>
<tr>
<td>Age Group (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-44 years</td>
<td>4.8</td>
<td>7.1</td>
<td>10.8</td>
<td>7.7</td>
</tr>
<tr>
<td>45-54 years</td>
<td>10.5</td>
<td>13.1</td>
<td>14.7</td>
<td>13.5</td>
</tr>
<tr>
<td>55-64 years</td>
<td>25</td>
<td>28.5</td>
<td>28.3</td>
<td>28.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54.86</td>
<td>56.23</td>
<td>55.14</td>
<td>37.33</td>
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<tr>
<td>Employee Relation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employee</td>
<td>65.59</td>
<td>66.52</td>
<td>65.61</td>
</tr>
<tr>
<td></td>
<td>Spouse</td>
<td>33.15</td>
<td>31.65</td>
<td>31.75</td>
</tr>
<tr>
<td></td>
<td>Child/Other</td>
<td>1.27</td>
<td>1.63</td>
<td>2.64</td>
</tr>
<tr>
<td>U.S. Census Region (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Northeast</td>
<td>20.42</td>
<td>20.09</td>
<td>8.42</td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>50.42</td>
<td>51.5</td>
<td>58.89</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>10.65</td>
<td>11.16</td>
<td>11.96</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0.18</td>
<td>0.16</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Compared with CKD stage 5, total costs are then more than four times higher during the incident chronic dialysis period. Much of this increase is for outpatient services. As shown in Table 2, which provides further detail by place of service, this primarily includes the center-based dialysis facilities. It also includes a large portion of outpatient hospital costs that are for dialysis-related services (estimated to be 65%), since some commercial insurers were billed for dialysis on outpatient hospital claims. However, there are also especially large absolute or relative increases in certain other cost components during the incident chronic dialysis period, notably for inpatient, emergency department, ambulatory surgical
Predictive Analytics & Modeling
WHAT DO WE NEED?

DATA
- Demographics
- Laboratory
- Claims
- Clinical Assessments
- Clinical Data Outside of Dialysis
- Outpatient Procedures and Visits
- Hospitalizations
- Treatment Related
- Patient Lifestyle/psychographic

SKILLS
- Clinical Expertise
- Data Analytics Expertise
- Operationalization
- Internal Statisticians
- External Statisticians

TECHNOLOGY
Predictive Analytics & Modeling

DATA

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Predictive Analytics & Modeling

STATISTICS

- Multivariate Adaptive Regression Spline (MARS)
- Supported Vector Machines (SVM)
- Decision Trees
- Random Forest
- Multiple regression models
- Predictors based on historical hospitalization rate
- Artificial Neural Networks (ANN)
- Least Absolute Shrinkage and Selection Operator

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Created a process for:

1. Assessment of modeling demand
2. Model prioritization through Predictive Analytics Steering Committee (PASC)
3. Creation of predictive models
4. Piloting and testing of predictive models
5. Deliver via API under FHIR standard
Predictive Analytics & Modeling

EFFORTS TO DATE

28 Requested
16 Given Go Ahead
12 Completed
3 In Progress
5 Actively Used
1 Not Started
YTD through May 2016 Manuscripts

- 14 In progress
- 12 Submitted
- 8 Published

Publication and Presentation
FMCNA Manuscripts

KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology
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Publication and Presentation
Symposium Presentations and Posters

ASN (n=31)

NKF (n=26)
VASA (n=5)

SHM (n=2)
IPNA (n=1)

ADC (n=4)
Health Form/AHA (n=2)

AVA (n=1)
ACHE Congress (n=2)

WSDS (n=2)
Critical Care Congress (n=1)

ANNA (n=1)
WIM (n=1)

IPNA (n=1)
HIMSS (n=1)

SHM

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Concluding Thoughts

My Three Principles for FMC Research Activities

– Contribute to advancing the science of medical care to people with high cost chronic illness

– Support broader relationships between FMC and the scientific community

– Develop a disciplined organization for supporting, conducting and reporting research