Perspectives on Research From a Dialysis Provider

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Fresenius Medical Care

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Disclosure of Interests

Franklin W. Maddux, MD FACP

Executive Vice President for Clinical & Scientific Affairs

Chief Medical Officer

Fresenius Medical Care North America

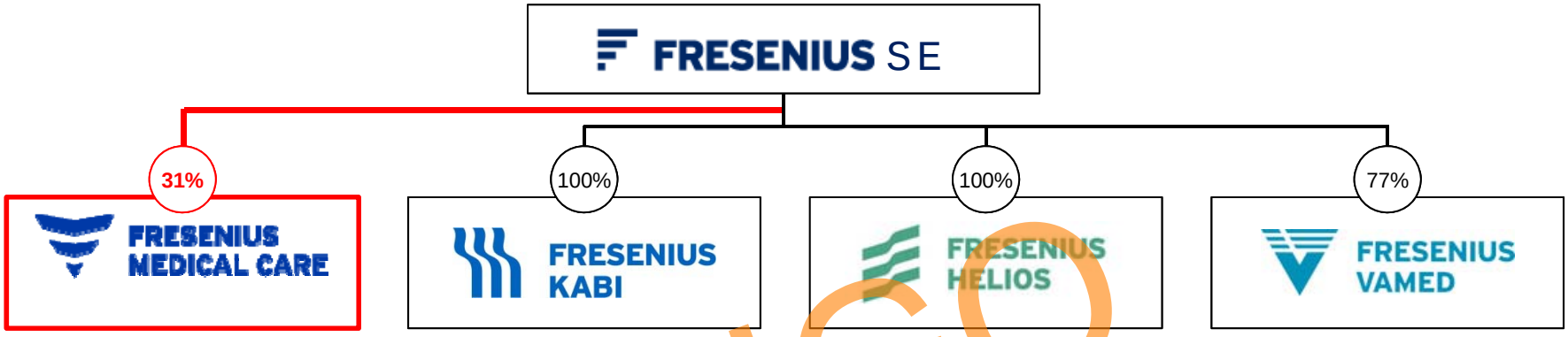
Disclosure:

Fresenius Medical Care	Employment
	Stock Ownership

The Next 30 Minutes

A Perspective from Fresenius Medical Care

The Fresenius Group



Fresenius SE Business Segments

	Overview
FRESENIUS MEDICAL CARE	• 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 KABI	• Offers infusion therapies, intravenously administered drugs and clinical nutrition • Transfusion & blood processing technologies
FRESENIUS HELIOS	• One of largest private hospital operators in Germany • 155 hospitals in Germany & Spain
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

Fresenius Medical Care North America

Assets Generating Data for Research

• Fresenius Kidney Care	Dialysis Services
• Sound Physicians	Acute Episodes of Care
• Fresenius Vascular Care	Interventional Radiology
• Fresenius Rx	Pharmacy
• Spectra Laboratories	Laboratory
• National Cardiovascular Partners	Cardiology
• Pacific Cardiology Associates	Cardiology
• Acumen Physician Solutions	Health IT Services
• Fresenius Physician Practice Services	Practice Management
• MedSpring Urgent Care	Urgent Care Practices
• Fresenius Health Partners	Health Insurance
• Frenova Renal Research	Clinical Research
• Fresenius Renal Therapies	Devices and Pharma
• Renal Research Institute	Biological Research

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

CLINICAL EPIDEMIOLOGY www.jasn.org

Heritability of Risk for Sudden Cardiac Arrest in ESRD

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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.

J Am Soc Nephrol 26: 2815–2820, 2015. doi: 10.1681/ASN.2014090881

Heritability of Sudden Cardiac Arrest in ESRD

JASN, Nov. 2015

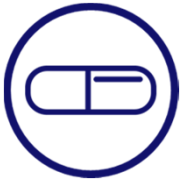
Figure 1. Higher prevalence of intrafamily cardiac arrest (patients) compared with matched unrelated pairs (controls). Family pairs: parent/child (*n*=1695), siblings (*n*=1602), cousin/uncle (*n*=756), or spouses (*n*=1064).

Observational Research Protocols

Fresenius Kidney Care Data Warehouse

>1.2 million ESRD patients

>300 million dialysis treatments



>1.2 billion medications administered

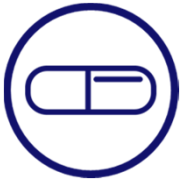
>1.3 billion lab results

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

Observational Research Protocols
Partners In MONDO

- Pontifical Catholic University of Parana, Brazil
- Imperial College, UK
- University of Maastricht, The Netherlands
- Hadassah Medical Center, Israel
- Kuratorium für Dialyse und Nierentransplantation (KfH), G
- 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

Observational Research Protocols
Countries Represented in MONDO

- 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
- Europe/Middle East
  - Israel
  - Italy
  - Netherlands
  - Portugal
  - Poland
  - Romania
  - Russia
  - Slovenia
  - Slovakia
  - Spain
  - Serbia
  - Sweden
  - Turkey
  - UAE
  - Ukraine
  - UK

BRIEF REVIEW www.jasn.org

TiME Trial Through May 2016

FMCNA Target Enrollment: 3216
FMCNA Enrollment: 3419

Pragmatic Trials in Maintenance Dialysis: Perspectives from the Kidney Health Initiative

Laura M. Dember,*† Patrick Archdeacon,‡§ Mahesh Krishnan,‖ Eduardo Lacson Jr.,¶ Shari M. Ling,** Prabir Roy-Chaudhury,†† Kimberly A. Smith,§ and Michael F. Flessner‡‡

Table 2. TiME Trial design

Design Element	Details
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

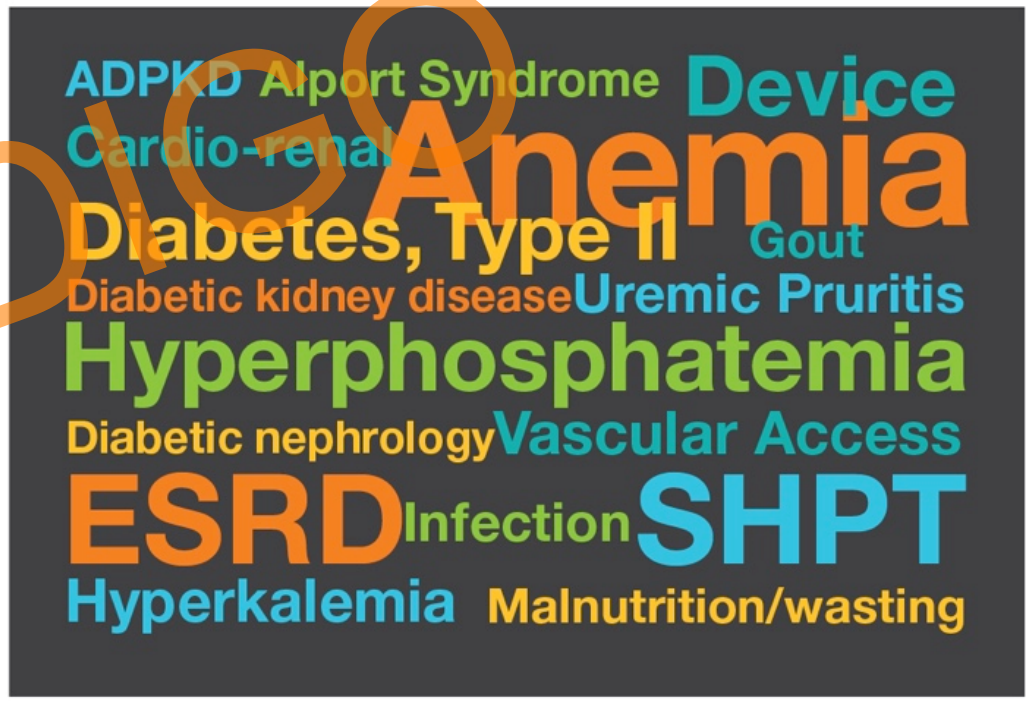
Pharma or Industry Sponsored Clinical Trials

Frenova Renal Research

Renal disease type

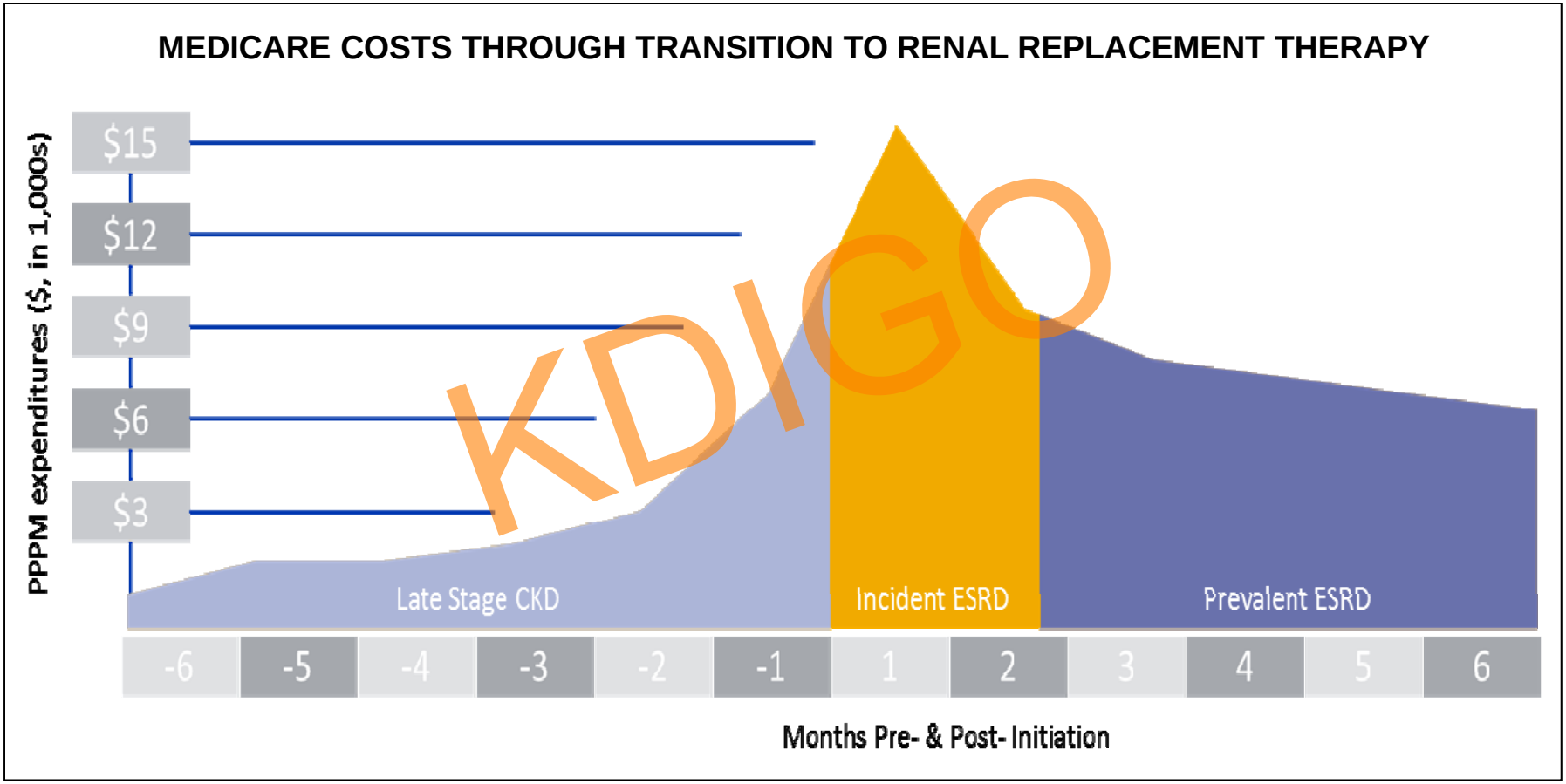
Disciplines

- 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



Analytical Insights Research

Analyzing the Patient Voice

FRESENIUS MEDICAL CARE

50,000
Patients

5.1 Million
Data Points

Analytical Insights Research

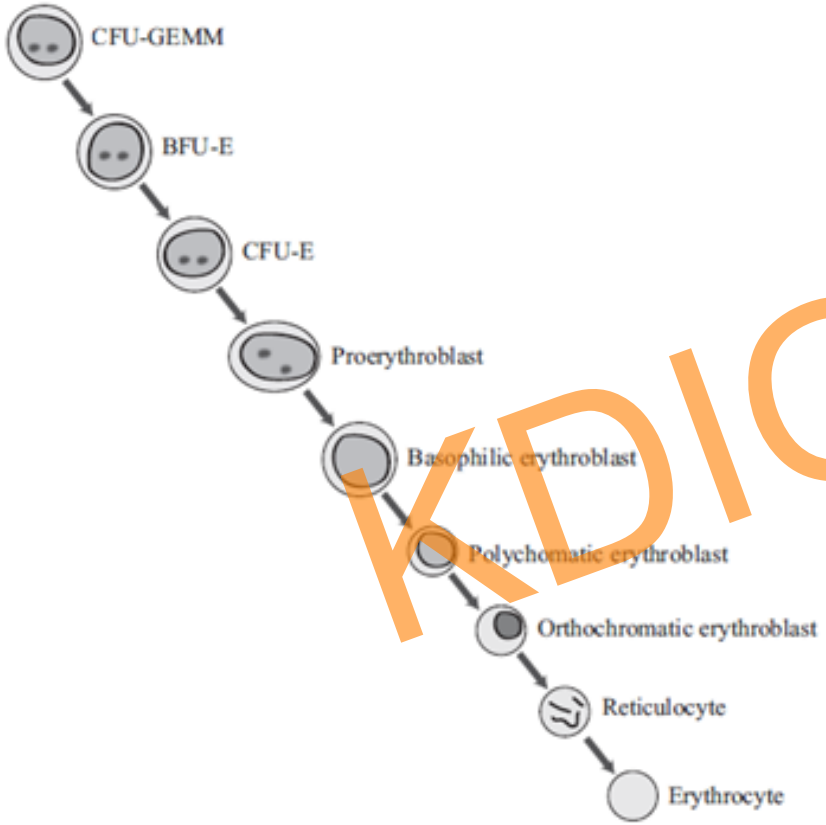
What Do ESRD Patients Care About?

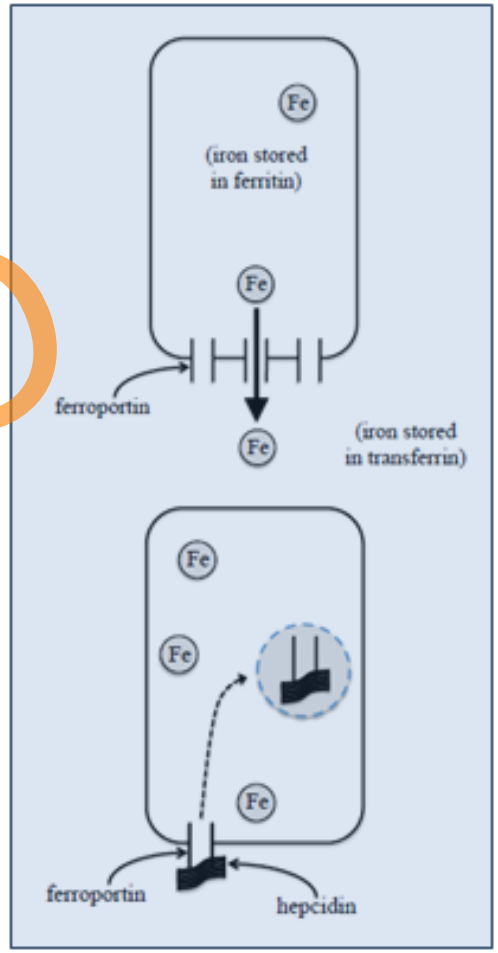
FRESENIUS MEDICAL CARE

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

Physiologic Modeling Research
Example: Anemia





Erythropoiesis cell lineage

Physiologic Modeling Research

Mathematical Modeling of the Anemia Patient Physiology

$$\frac{\partial}{\partial t}\int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu} P(t,\xi,\zeta)d\xi d\zeta = 2(\text{rate entering iron class } \gamma \text{ from class } 2\gamma)$$

$$- (\text{rate of cells leaving iron class } \gamma)$$
$$- (\text{death rate}) + (\text{rate of maturation in})$$
$$- (\text{rate of maturation out})$$
$$+ (\text{rate of hemoglobinization in})$$
$$- (\text{rate of hemoglobinization out})$$

$$= 2\int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu} \beta P(t,\xi,2\zeta)d\xi d\zeta$$
$$- \int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu} \beta P(t,\xi,\zeta)d\xi d\zeta$$
$$- \int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu} \delta P(t,\xi,\zeta)d\xi d\zeta$$
$$+ \int_{\gamma}^{\gamma+\Delta\gamma} \rho P(t,\mu,\zeta)d\zeta - \int_{\gamma}^{\gamma+\Delta\gamma} \rho P(t,\mu+\Delta\mu,\zeta)d\zeta$$
$$+ \int_{\mu}^{\mu+\Delta\mu} hP(t,\xi,\gamma)d\xi - \int_{\mu}^{\mu+\Delta\mu} hP(t,\xi,\gamma+\Delta\gamma)d\xi,$$

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

Clinical Comparative Effectiveness

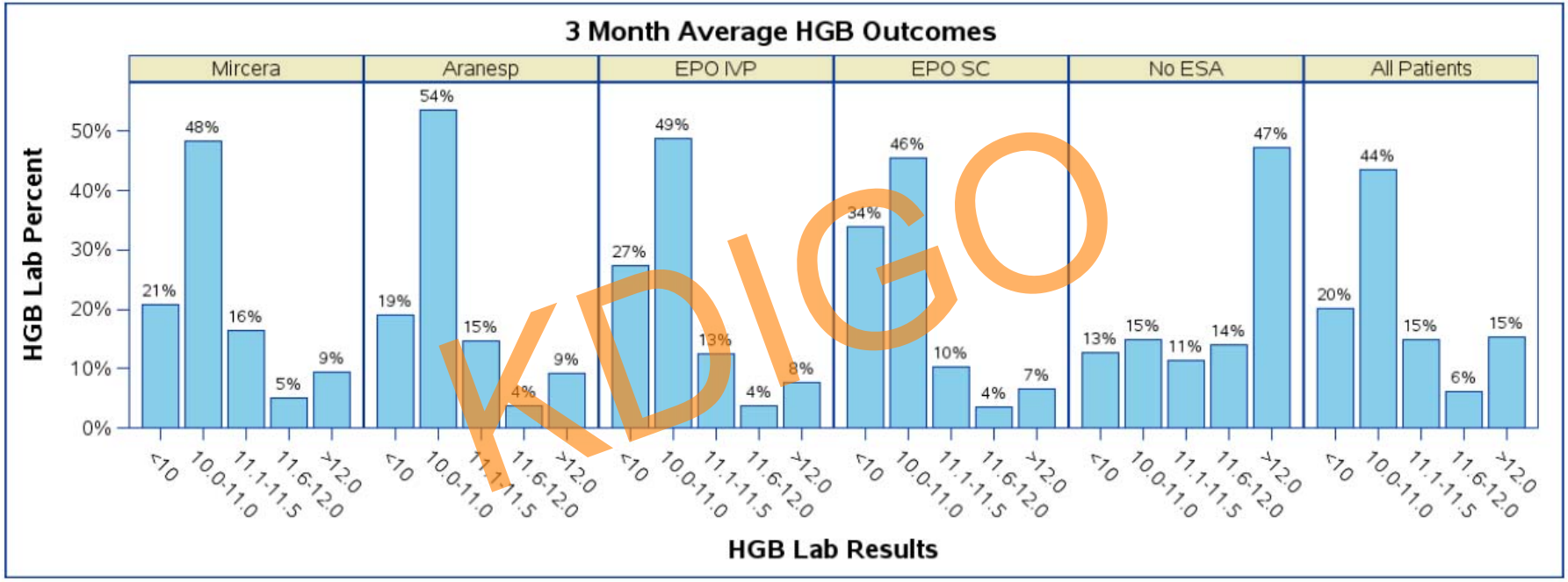
The Four Quad Plot

FMCNA anemia management value proposition chart for ESA

Concurrent Observational Analysis

Hemoglobin Performance

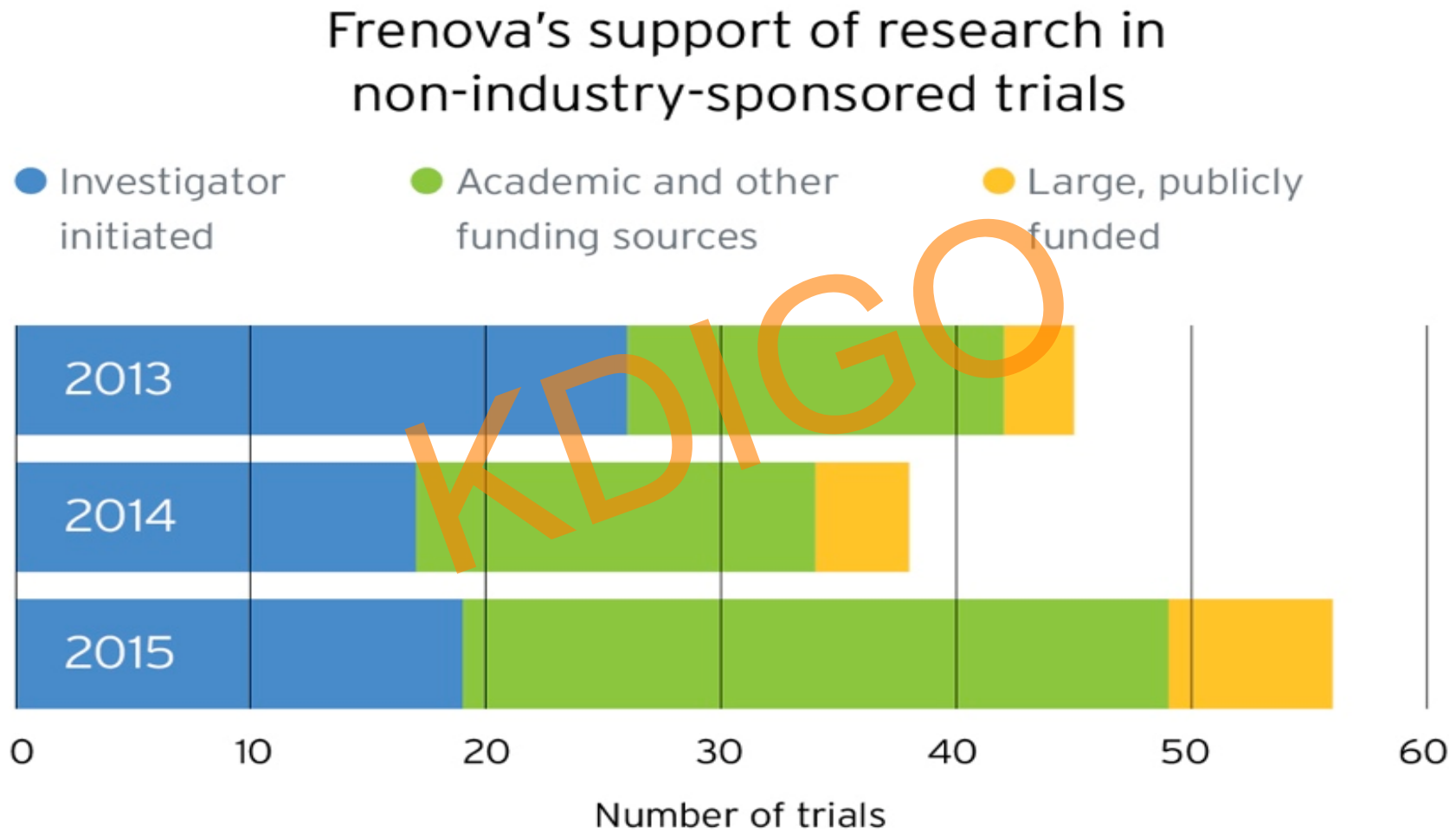
HGB 3 Month and 1 Month Outcome [1]



69% **66%**

10-12 g/dL

Investigator Initiated Studies

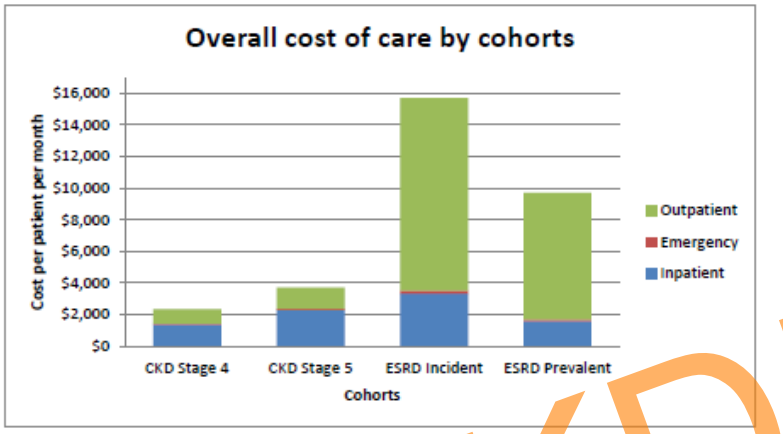


Source: 2015 FMCNA data

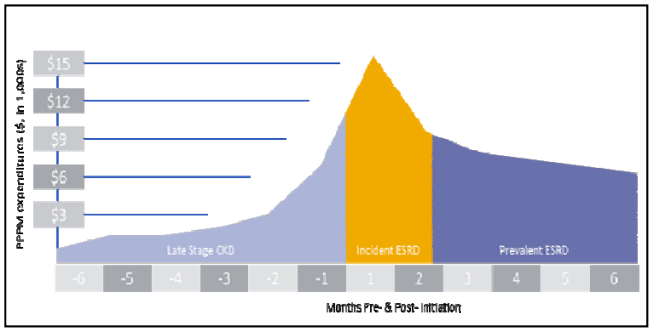
Licensing De-identified Data for Research

Studying Transition of Care Costs

Figure 2: Overall Cost of Care by Cohort



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 3, which provides further detail by place of service, this primarily includes the services billed by ESRD 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



Results

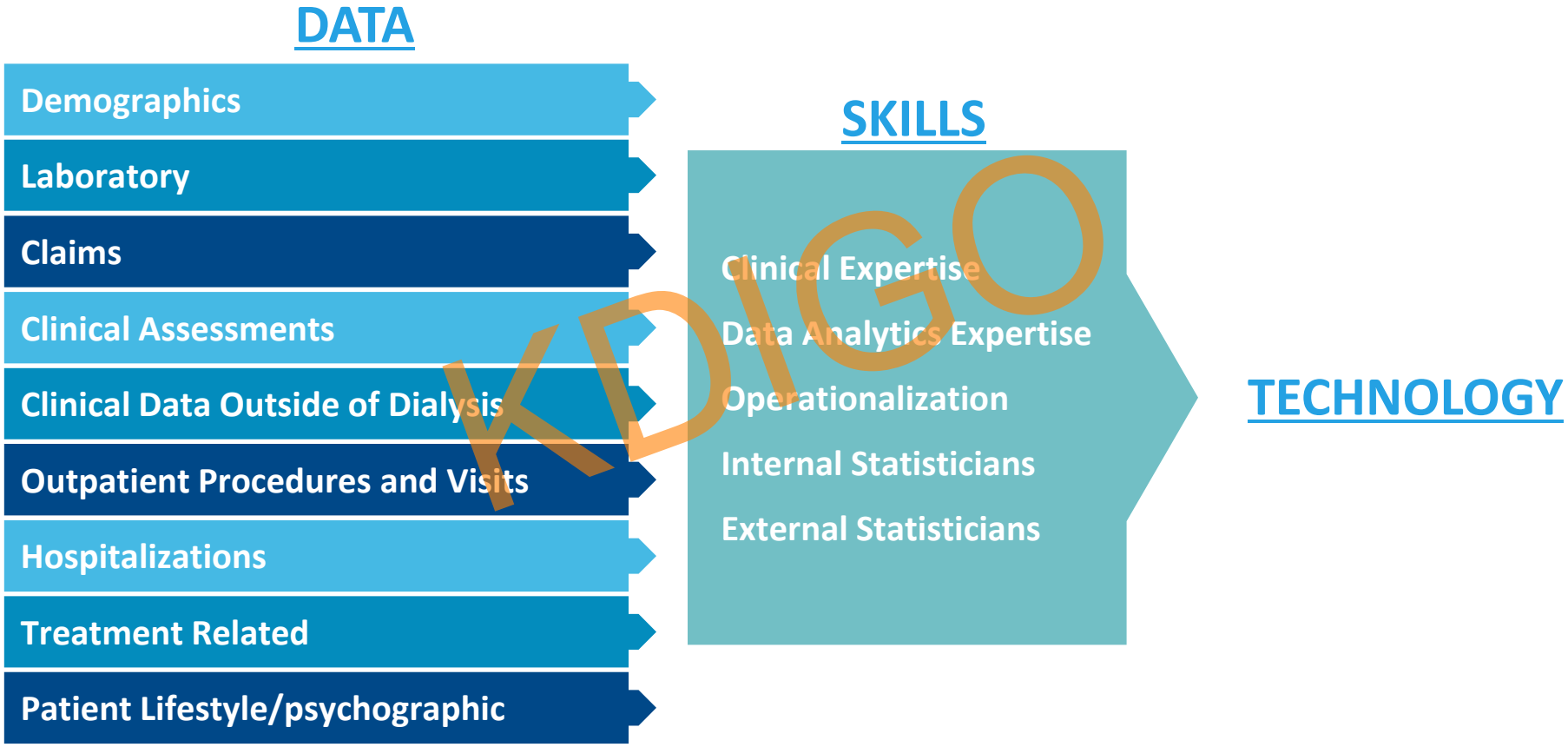
The characteristics of the four cohorts defined for this study are described in Table 1. Each cohort includes between 14,000 and 31,000 patients. Close to half or more of the patients in each cohort are between the ages of 55 and 64. Patients are approximately twice as likely to have coverage through 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 enrollees 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

	CKD Stage 4	CKD Stage5	ESRD Incident	ESRD Prevalent
Number of Patients	31,540	14,243	14,215	22,926
Mean follow up months	10.5	7.5	3.0	12.4
Age* (Mean(SD))	54.0 (9.3)	52.2(10.0)	50.5(11.0)	52.0(10.2)
Age Group (%)				
18-34 years	4.8	7.1	10.8	7.7
35-44 years	10.5	13.1	14.7	13.5
45-54 years	25	28.5	28.3	28.2
55-64 years	59.7	51.3	46.1	50.6
Male(%)	54.86	56.23	56.14	57.35
Employee Relation (%)				
Employee	65.59	66.52	65.61	63.29
Spouse	33.15	31.85	31.75	34.34
Child/Other	1.27	1.63	2.64	2.36
U.S. Census Region (%)				
Northeast	10.42	10.99	8.42	10.11
North Central	28.34	26.19	24.72	24.62
South	50.42	51.5	53.89	53.49
West	10.65	11.16	11.96	11.48
Unknown	0.18	0.16	1.01	0.3

Predictive Analytics & Modeling

WHAT DO WE NEED?



Predictive Analytics & Modeling

DATA

Predictive Analytics & Modeling

STATISTICS

Predictive Analytics & Modeling
PROCESS

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

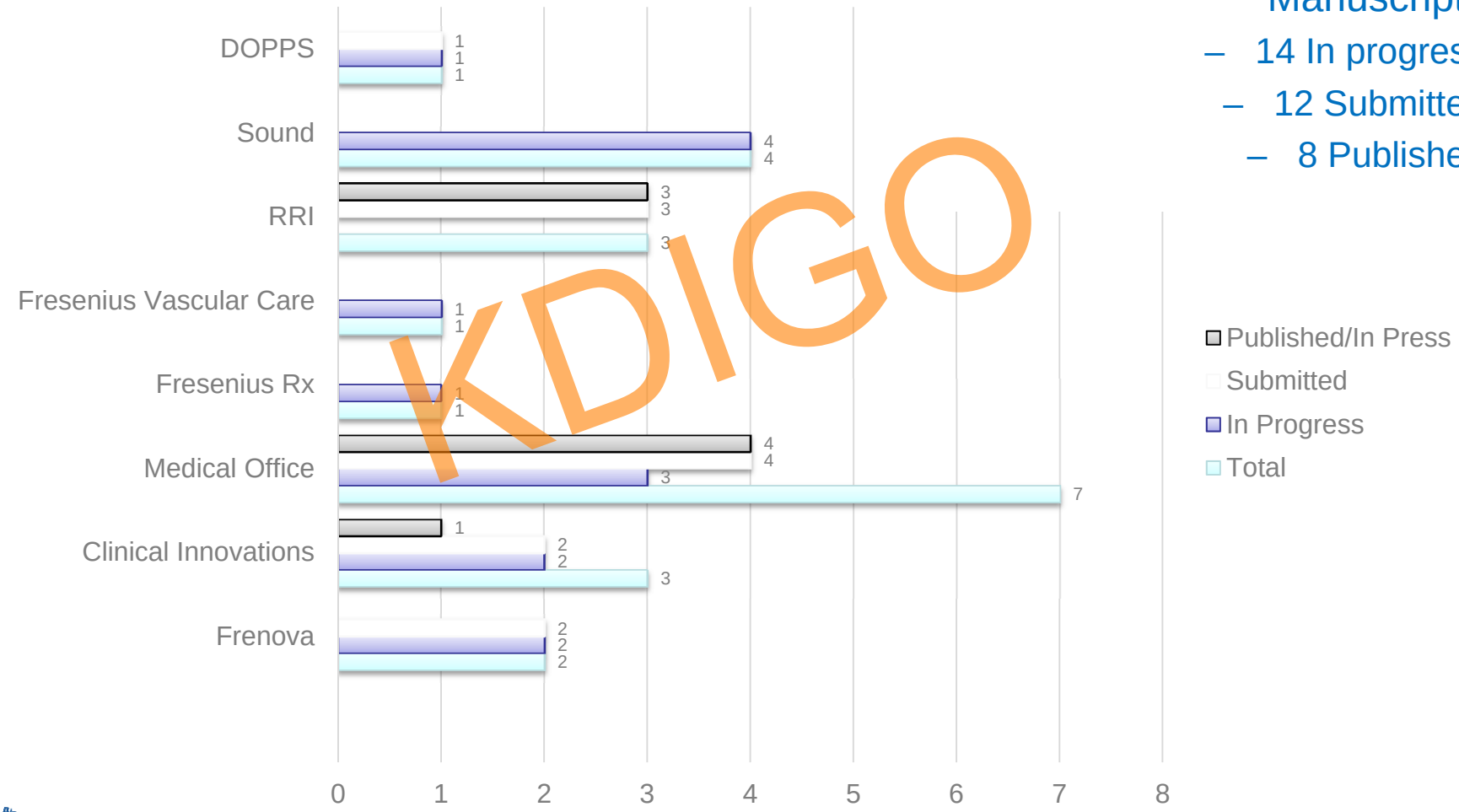
EFFORTS TO DATE

Publication and Presentation

FMCNA Manuscripts

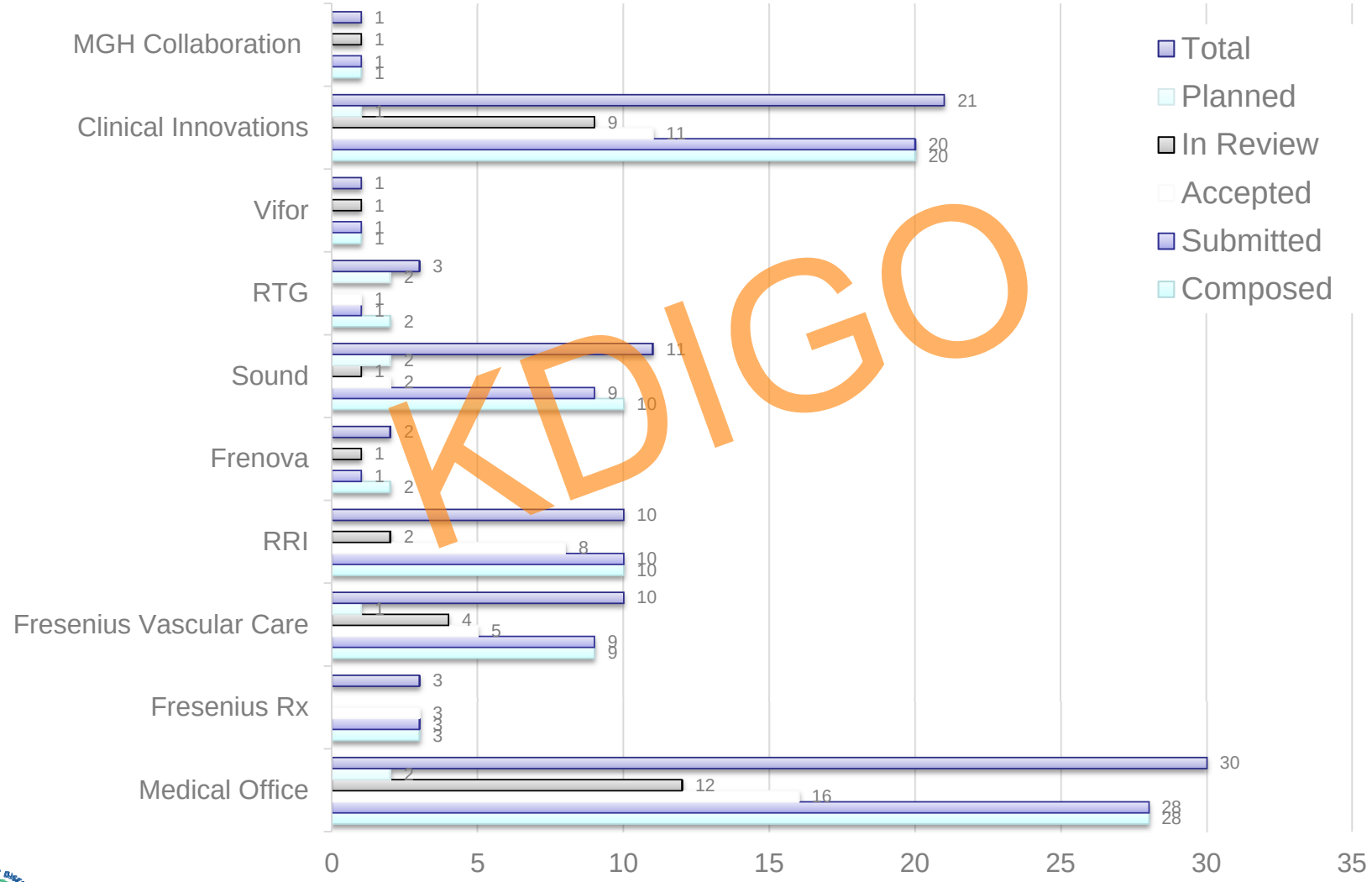
YTD through May 2016 Manuscripts

- 14 In progress
- 12 Submitted
- 8 Published



Publication and Presentation of Abstracts

86 Accepted / 8 Planned YTD 2016

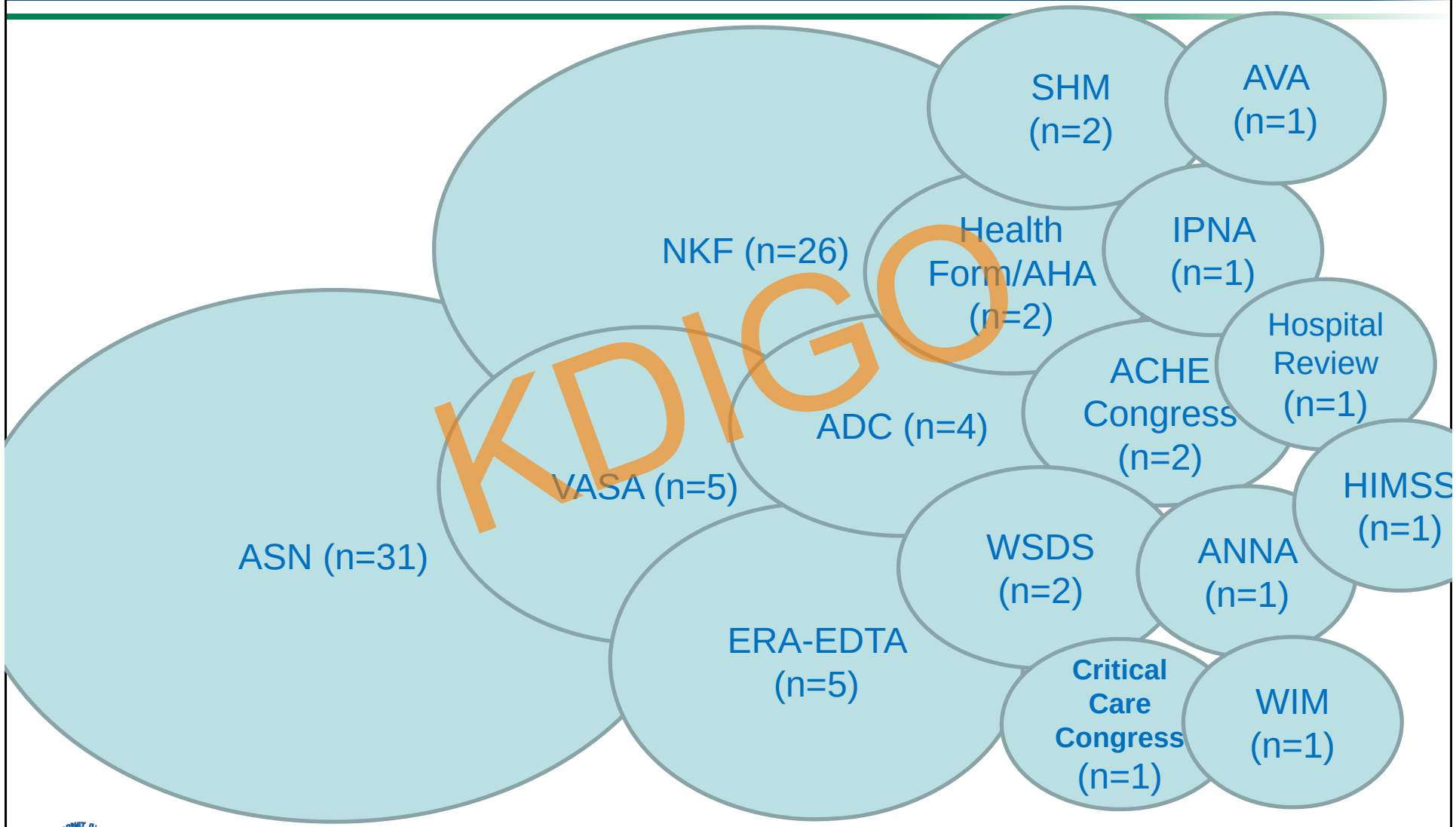


KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology

September 8-11, 2016 | Paris, France

Publication and Presentation

Symposium Presentations and Posters



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