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Rare diseases in Primary Care: Prevalence and Practice

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Keywords: Rare disease, primary care, scope of practice

Abstract

Objectives: There are more than 7,000 rare diseases in the US and they are prevalent in 8% of the population. Due to life-threatening risk and limited therapies, early detection and treatment are critical. The purpose of this study was to explore characteristics of visits for patients with rare diseases seen by primary care physicians (PCPs).

Design: The study used a cross sectional study using a national representative dataset, the National Ambulatory Medical Care Survey for the years 2012-2014.

Setting: Primary care setting

Participants: Visits to PCPs (n= 22,306 representing 354,507,772 office visits to PCPs).

Primary Outcome Measures: Prevalence of rare diseases in visits of PCPs was the primary outcome. Bivariate analyses and logistic regression analyses were used to compare patients with rare diseases and those without rare diseases and examined characteristics of PCP visits for rare diseases and practice pattern.

Results: Among outpatient visits to PCPs, rare diseases account for 1.6% of the visits. The majority of patients with rare diseases were established patients (93.0%) and almost half (49.0%) were enrolled in public insurance programs. The time spent in visits for rare diseases (22.4 minutes) and visits for more common diseases (21.3 minutes) was not significantly different (p=.09). In an adjusted model controlling for patient characteristics (age, sex, types of insurance, reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with

rare diseases were 34% less likely to be referred to another provider (OR 0.66, 95% CI, 0.44-0.99).

Conclusions: Visits for rare diseases are uncommon in primary care practice. Future research may help to explain whether this low level of management of rare diseases in primary care practice is consistent with a goal of a broad scope of care.

Strengths and limitations of this study

- This study is the first research to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.
- The study used population-based national representative data allowing for generalizability.
- Primary care physicians may play a vital role in providing continuous care and managing patients with rare diseases effectively.
- The study is limited to the actions recorded in one visit due to study design.
- The study was unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care

Introduction

Primary Care Physicians (PCPs) are trained to provide care for a broad scope of conditions within their patient population. When PCPs maintain a broad scope of practice this safeguards access and quality of care for the general population. Some of these conditions are managed directly by the PCP and with others the PCP coordinates the care for the patient. One recent study indicated that in one year, family physicians typically manage about 1,700 diagnoses in office visits, with 100 diagnoses managed frequently.(1)

In addition to common, high prevalence diseases like diabetes, hypertension and arthritis, a substantial proportion of the general patient population, has a rare disease, or diseases. As of 2017, the National Institute of Health (NIH) Genetic and Rare Disease Information Center (GARD) had identified 7,000 rare diseases, affecting approximately 25-30 million people in the US population. (2) Rare diseases are categorized as life-threatening, with only few limited effective therapies available. In addition to the emotional and physical burden associated with diagnosis, patients with a rare disease often face financial burden due to the significant cost associated with drugs and therapies. As such, early detection and treatment are critical. For example, in one study, more than half of patients with rare diseases being seen at a PCP practice had been diagnosed with rare diseases at a PCP practice.(3)

However, to date there have been few studies investigating the role of PCPs in the management of patients with rare diseases. The purpose of this study was to

examine in a nationally representative sample of visits, the prevalence of rare diseases cared for in primary care practice as well as characteristics of patients and providers.

Methods

This study used the National Ambulatory Medical Care Survey (NAMCS), a national representative dataset, for the years 2012-2014. The NAMCS is a national probability sample survey of ambulatory medical care visits to office-based physicians that allows for national estimates regarding medical care in the US.(3) NAMCS data is collected annually by the National Center for Health Statistics (NCHS). The sample frame for NAMCS data in the years 2012-2014 was composed of PCPs who specialize in primary care (e.g., General and Family Practice, Internal medicine and Pediatrics), and who identified themselves as the primary care physician (PCP) of the patient.(4) This list conforms to the definition used by the NAMCS to categorize primary care. The unweighted sample size was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014.

Rare disease

A rare disease is defined as a case that affects fewer than 200,000 people.(2) For this study, diagnoses were identified as a rare disease using the list provided by the GARD Information Center.(2)

Independent Variables

Demographics of patients seen by PCPs, such as age, gender and race/ethnicity, were used. Gender and race/ethnicity (i.e., Non-Hispanic White, Non-Hispanic Black, Hispanics and Others) were considered categorical variables whereas age was used as

a continuous variable. In addition, their form of health insurance, major reason for the visit, and total number of diagnosed chronic diseases were included as categorical variables. Health insurance was stratified into four categories: private insurance, public insurance such as Medicaid and Medicare, self-pay, and others. Major reason for the visit was also categorized into four groups: new problems, chronic problems, pre- or post-surgery care and preventive care.

Providers characteristics including practice location (i.e., urban or rural), referral to other providers (i.e., yes or no) were examined. Time spent with providers in primary care setting was compared between patients with rare diseases and those without rare diseases.

Statistical Analysis

To account for the complex survey design used in the NAMCS, a weighted variable was used to consider survey design effect. This allows for us to provide population estimates of United States ambulatory health care utilization.(3) The prevalence of rare disease seen in the primary care setting was estimated. Chi-square tests were used to compare characteristics of PCPs who care for rare diseases against those who do not. Logistic regression was also employed to examine the association between PCP referral to other providers and patient diagnosis of a rare disease. All analyses were conducted in SAS version 9.4 (Cary, NC). This study was approved as exempt by the Institutional Review Board at the University of Florida.

Patient and Public Involvement

Patients and/or public were not involved in this study.

Results

The final sample was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014. A total of 1,508 PCPs participated to submit data for sample patient visits. Of the total patient visits to a PCP, a rare disease was noted in 1.6% of those visits. PCPs cared for 177 different rare diseases. Patients with rare diseases were significantly older than those without rare diseases (age difference = 8.3 years, p<.01), while no significant differences were found in the distribution of sex and race/ethnicity (Table 1). The majority of patients with rare diseases were established patients (93.0%), having been seen by the PCP more than one time, and almost half (49.3%) were enrolled in private insurance programs. Of the visits for patients diagnosed with a rare disease, 39.0% visited their PCPs with a comorbid chronic problem. In addition, they had a higher total number of chronic diseases compared to patients without rare diseases (Table 1).

Of visits by patients with rare disease, 14.3% were referred to other providers (Table 2). While PCPs spent slightly more time with their patients who had rare diseases (22.4 min), compared to patients without rare diseases (21.3 min), it was not significantly different (Table 2). The majority of visits for patients with rare diseases and more common diseases who were seen by PCPs were located in urban areas. PCPs practicing in rural areas (7.6%) were not significantly less likely than PCPs practicing in urban areas (16.8%; p=.06) to refer patients with rare diseases to another physician. In a bivariate analysis, care for rare disease was also not associated with rurality (p=.32) (Table 2).

In an unadjusted regression model, patients with rare diseases were 41% less likely to be referred to other providers than those without rare diseases. After controlling for covariates, such as patients characteristics (i.e., age, sex, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with rare diseases were 64% less likely to be referred to another provider (Table 3).

Discussion

This study found that few patients with a rare disease were identified as being managed in primary care practice. Patients with rare diseases show significantly different characteristics compared to those without a rare disease diagnosis. Not surprisingly, visits in primary care for patients with rare diseases are more likely than patients without rare diseases to lead to referral to another provider. To our knowledge, this is the first study to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.

Much of medical practice and the corresponding comfort in diagnosing and treating conditions is affected by the frequency of occurrence of the condition and pattern recognition. Rare diseases are by their very nature uncommon and thus PCPs may not always feel comfortable with the nuances of treatment and potential complications for a disease that they encounter very infrequently. According to the National Academy of Medicine, since rare diseases tend to accompany multiple common conditions, it disrupts a clinician's ability to recognize clues of rare diseases.(7) In many of these cases PCPs need more than a consult from a specialist, especially when the primary

care team does not have the specialized medical knowledge. Receiving all of their care from specialists may not be the best situation for the patient. Patients with rare diseases need to be managed in primary care or at least have shared care between primary care and specialists in complementary roles to provide a more effective management of these complex patients.

There are some limitations to this study. First, due to the design of the NAMCS we are limited to the actions recorded in that one visit. The design does allow us to have an understanding of the types of patients seen in primary care but it is not data on a cohort of patients. Thus, we do not know what sort of care may have transpired between the patient and the physician in previous visits. Second, we are able to see if patients are referred in that one visit, we are unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care.

Conclusion

This study identified characteristics of patients with rare diseases who are seen in primary care practice and the delivery patterns of PCPs managing patients with rare diseases. Findings from this study suggest that PCPs must possess a broad scope of practice in order to deliver comprehensive, high-quality care. A better understanding of the overall management of patients with rare diseases managed solely outside of primary care would help to improve the care for these patients.

Acknowledgements

Contributors:

Ara Jo, PhD led the entire research as the first and corresponding author from writing the manuscript, analyzing the data and interpretation.

Samantha Larson, MPH, analyzed the data and contributed to writing the manuscript.

Peter J. Carek, MD, MS contributed to writing the manuscript.

Michael R. Peabody, PhD, contributed to writing the manuscript.

Lars E. Peterson, MD, PhD, contributed to writing the manuscript.

Arch G. Mainous III, PhD, contributed to writing the manuscript and guided the direction of the study.

Conflict of Interest: Drs. Peterson and Peabody are employees of the American Board of Family Medicine. No other authors have no declaration of conflict of interests.

Funding Statement: This work was supported by a grant from the American Board of Family Medicine Foundation.

Ethics approval: This study was approved as exempt by the Institutional Review Board at the University of Florida.

Data sharing statement: Data are available through the National Ambulatory Medical Care Survey access from https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm.

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Table 1. Characteristics of Patients with Rare Diseases in Primary Care, NAMCS 2012-2014 (unweighted N= 22,306, weighted N= 354,507,772)

	Patients with rare diseases (%)	Patients without rare diseases (%)	p-value
Unweighted Sample Size	363	21,943	
Weighted Sample Size	5,581,791	348,925,981	
Age (year-old) **	47.7	39.4	<0.001
Sex			
Female	56.4	53.8	0.44
Race			
Non-Hispanic White	75.0	70.6	0.54
Non-Hispanic Black	8.6	10.1	
Hispanics	11.7	14.3	
Others	4.7	5.0	
Insurance Types			
Private Insurance	49.3	54.6	0.15
Public Insurance	47.3	40.0	
Self-pay	1.8	3.5	
Other	1.5	1.9	
Major reasons for this visit**			
New Problems	33.7	42.6	0.002
Chronic Problems	39.0	28.7	
Pre-/Post-Surgery	27.3	28.7	
Preventive Care	0.0	0.0	
Total Number of Chronic Diseases**	1.3	1.0	0.001

** statistical significant level at .05

Table 2. Practice Characteristics of Primary Care Physicians who Care for Patients with Rare Diseases using NAMCS, 2012-2014

	Patients with rare diseases	Patients without rare diseases	p-value
Practicing Area			
Urban	84.5	86.4	0.32
Rural	15.5	13.6	
Referral to Other Providers**			
Yes	14.3	9.0	0.01
No	85.7	91.0	
Time Spent with Providers (min)	22.4	21.3	0.09

** statistical significant level at .05

Table 3. Odds Ratios of Referral Using Unadjusted and Adjusted Logistic Regression Analyses using NAMCS, 2012-2014

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Not having a rare disease	Reference	Reference
Having a rare disease	0.59 (0.40-0.87)**	0.66 (0.44-0.99)**

*Controlled for age, gender, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established vs. new patient.

** statistical significant level at .05

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	n/a
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5-6
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	7-8, 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and Practice for Rare diseases in Primary Care

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Abstract

Objectives: There are more than 7,000 rare diseases in the US and they are prevalent in 8% of the population. Due to life-threatening risk and limited therapies, early detection and treatment are critical. The purpose of this study was to explore characteristics of visits for patients with rare diseases seen by primary care physicians (PCPs).

Design: The study used a cross sectional study using a national representative dataset, the National Ambulatory Medical Care Survey for the years 2012-2014.

Setting: Primary care setting

Participants: Visits to PCPs (n= 22,306 representing 354,507,772 office visits to PCPs).

Primary Outcome Measures: Prevalence of rare diseases in visits of PCPs was the primary outcome. Bivariate analyses and logistic regression analyses were used to compare patients with rare diseases and those without rare diseases and examined characteristics of PCP visits for rare diseases and practice pattern.

Results: Among outpatient visits to PCPs, rare diseases account for 1.6% of the visits. The majority of patients with rare diseases were established patients (93.0%) and almost half (49.0%) were enrolled in public insurance programs. The time spent in visits for rare diseases (22.4 minutes) and visits for more common diseases (21.3 minutes) was not significantly different (p=.09). In an adjusted model controlling for patient characteristics (age, sex, types of insurance, reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with

rare diseases were 52% more likely to be referred to another provider (OR 1.52, 95% CI, 1.01-2.28).

Conclusions: Visits for rare diseases are uncommon in primary care practice. Future research may help to explain whether this low level of management of rare diseases in primary care practice is consistent with a goal of a broad scope of care.

Strengths and limitations of this study

- This study is the first research to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.
- The study used population-based national representative data allowing for generalizability.
- Primary care physicians may play a vital role in providing continuous care and managing patients with rare diseases effectively.
- The study is limited to the actions recorded in one visit due to study design.
- The study was unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care

Introduction

Primary Care Physicians (PCPs) are trained to provide care for a broad scope of conditions within their patient population. When PCPs maintain a broad scope of practice this safeguards access and quality of care for the general population. Some of these conditions are managed directly by the PCP and with others the PCP coordinates the care for the patient. One recent study indicated that in one year, family physicians typically manage about 1,700 diagnoses in office visits, with 100 diagnoses managed frequently.(1)

In addition to common, high prevalence diseases like diabetes, hypertension and arthritis, a substantial proportion of the general patient population, has a rare disease, or diseases. As of 2017, the National Institute of Health (NIH) Genetic and Rare Disease Information Center (GARD) had identified 7,000 rare diseases, affecting approximately 25-30 million people in the US population. (2) Rare diseases are categorized as life-threatening, with only few limited effective therapies available. In addition to the emotional and physical burden associated with diagnosis, patients with a rare disease often face financial burden due to the significant cost associated with drugs and therapies. As such, early detection and treatment are critical. For example, in one study, more than half of patients with rare diseases being seen at a PCP practice had been diagnosed with rare diseases at a PCP practice.(3)

However, to date there have been few studies investigating the role of PCPs in the management of patients with rare diseases. The purpose of this study was to

examine in a nationally representative sample of visits, the prevalence of rare diseases cared for in primary care practice as well as characteristics of patients and providers.

Methods

This study used the National Ambulatory Medical Care Survey (NAMCS), a national representative dataset, for the years 2012-2014. The NAMCS is a national probability sample survey of ambulatory medical care visits to office-based physicians that allows for national estimates regarding medical care in the US.(3) NAMCS data is collected annually by the National Center for Health Statistics (NCHS). The sample frame for NAMCS data in the years 2012-2014 was composed of PCPs who specialize in primary care (e.g., General and Family Practice, Internal medicine and Pediatrics), and who identified themselves as the primary care physician (PCP) of the patient.(4) This list conforms to the definition used by the NAMCS to categorize primary care. Diagnosis was determined based upon the ICD-9 codes and the diagnosis made by a PCP at a visit was electronically recorded in the patient record form. The patient report form provided preexisting conditions, current diagnosis and new diagnosis. (5) Thus, more than 30 diagnoses can be managed via this report form. (6) Furthermore, this report form allows us to identify established patients who have visited before whereas it does not allow us to estimate numbers of previous visits. The unweighted sample size was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014.

Rare disease

A rare disease is defined as a disease or a disorder that affects fewer than 200,000 people in the US.(2, 7) For this study, diagnoses were identified as a rare disease using

the list provided by the GARD Information Center.(2) Two independent researchers and (i.e., Dr. Jo and Larson) and one family medicine physician (i.e., Dr. Carek) reviewed all new diagnosis in designated study years and identified rare diseases by comparing the list of GARD. With consensus agreements, rare diseases for the study were determined.

Independent Variables

Demographics of patients seen by PCPs, such as age, gender and race/ethnicity, were used. Gender and race/ethnicity (i.e., Non-Hispanic White, Non-Hispanic Black, Hispanics and Others) were considered categorical variables whereas age was used as a continuous variable. In addition, their form of health insurance, major reason for the visit, and total number of diagnosed chronic diseases were included as categorical variables. Health insurance was stratified into four categories: private insurance, public insurance such as Medicaid and Medicare, self-pay, and others. Major reason for the visit was also categorized into four groups: new problems, chronic problems, pre- or post-surgery care and preventive care.

Providers' characteristics including practice location (i.e., urban or rural), referral to other providers (i.e., yes or no) were examined. Time spent with providers in primary care setting was compared between patients with rare diseases and those without rare diseases.

Statistical Analysis

To account for the complex survey design used in the NAMCS, a weighted variable was used to consider survey design effect. This allows for us to provide national estimates of

United States ambulatory health care visits to office-based physicians and community health centers.(3) Also, it allows us to produce national estimates of the ambulatory health care utilization in the US (3). The prevalence of rare disease seen in the primary care office visit was estimated. Chi-square tests were used to compare characteristics of PCPs who care for rare diseases against those who do not. Logistic regression was also employed to examine the association between PCP referral to other providers and patient diagnosis of a rare disease. All analyses were conducted in SAS version 9.4 (Cary, NC). This study was approved as exempt by the Institutional Review Board at the University of Florida.

Patient and Public Involvement

Patients and/or public were not involved in this study.

Results

The final sample was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014. A total of 1,508 PCPs participated to submit data for sample patient visits. Of the total patient visits to a PCP, a rare disease was noted in 1.6% of those visits. PCPs cared for 177 different rare diseases. Patients with rare diseases were significantly older than those without rare diseases (age difference = 8.3 years, $p<.01$), while no significant differences were found in the distribution of sex and race/ethnicity (Table 1). The majority of patients with rare diseases were established patients (93.0%), having been seen by the PCP more than one time, and almost half (49.3%) were enrolled in private insurance programs. Of the visits for patients diagnosed with a rare disease, 39.0% visited their PCPs with a comorbid chronic

problem. In addition, they had a higher total number of chronic diseases compared to patients without rare diseases (Table 1).

Of visits by patients with rare disease, 14.3% were referred to other providers (Table 2). While PCPs spent slightly more time with their patients who had rare diseases (22.4 min), compared to patients without rare diseases (21.3 min), it was not significantly different (Table 2). The majority of visits for patients with rare diseases and more common diseases who were seen by PCPs were located in urban areas. PCPs practicing in rural areas (7.6%) were not significantly less likely than PCPs practicing in urban areas (16.8%; p=.06) to refer patients with rare diseases to another physician. In a bivariate analysis, care for rare disease was also not associated with rurality (p=.32) (Table 2).

In an unadjusted regression model, patients with rare diseases were 69% more likely to be referred to other providers than those without rare diseases. After controlling for covariates, such as patients' characteristics (i.e., age, sex, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with rare diseases were 52% more likely to be referred to another provider than those without rare diseases (Table 3).

Discussion

This study found that few patients with a rare disease were identified as being managed in primary care practice. Patients with rare diseases in the primary care setting show significantly older and have more comorbidities compared to those without a rare disease diagnosis whereas patients with rare diseases are comparable to those without

rare diseases in terms of sex distribution, race/ethnicity and types of health insurance. Not surprisingly, visits in primary care for patients diagnosed with rare diseases are more likely than patients without rare diseases to lead to referral to another provider. To our knowledge, this is the first study to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.

Much of medical practice and the corresponding comfort in diagnosing and treating conditions is affected by the frequency of occurrence of the condition and pattern recognition. Rare diseases are by their very nature uncommon and thus PCPs may not always feel comfortable with the nuances of treatment and potential complications for a disease that they encounter very infrequently. According to the National Academy of Medicine, since rare diseases tend to accompany multiple common conditions, it disrupts a clinician's ability to recognize clues of rare diseases.(8) In many of these cases PCPs need more than a consult from a specialist, especially when the primary care team does not have the specialized medical knowledge. Receiving all of their care from specialists may not be the best situation for the patient. Patients with rare diseases need to be managed in primary care or at least have shared care between primary care and specialists in complementary roles to provide a more effective management of these complex patients.

There are some limitations to this study. First, due to the design of the NAMCS we are limited to the actions recorded in that one visit. The design does allow us to have an understanding of the types of patients seen in primary care but it is not data on a cohort of patients. Thus, we do not know what sort of care may have transpired between the

patient and the physician in previous visits. Also, it is not able to explore the linkage of multiple consultations with specialists pre- or post-visit to PCPs. Second, we are able to see if patients are referred in that one visit, we are unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care.

Conclusion

This study identified characteristics of patients with rare diseases who are seen in primary care practice and the delivery patterns of PCPs managing patients with rare diseases. Findings from this study suggest that PCPs must possess a broad scope of practice in order to deliver comprehensive, high-quality care. A better understanding of the overall management of patients with rare diseases managed solely outside of primary care would help to improve the care for these patients.

Acknowledgements

Contributors:

Ara Jo, PhD led the entire research as the first and corresponding author from writing the manuscript, analyzing the data and interpretation.

Samantha Larson, MPH, analyzed the data and contributed to writing the manuscript.

Peter J. Carek, MD, MS contributed to writing the manuscript.

Michael R. Peabody, PhD, contributed to writing the manuscript.

Lars E. Peterson, MD, PhD, contributed to writing the manuscript.

Arch G. Mainous III, PhD, contributed to writing the manuscript and guided the direction of the study.

Conflict of Interest: Drs. Peterson and Peabody are employees of the American Board of Family Medicine. No other authors have no declaration of conflict of interests.

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Table 1. Characteristics of Patients with Rare Diseases in Primary Care, NAMCS 2012-2014 (unweighted N= 22,306, weighted N= 354,507,772)

	Patients with rare diseases (%)	Patients without rare diseases (%)	p-value
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Weighted Sample Size	5,581,791	348,925,981	
Mean Age (year-old) **	47.7	39.4	<0.001
Sex			
Female	56.4	53.8	0.44
Race			
Non-Hispanic White	75.0	70.6	0.54
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Hispanics	11.7	14.3	
Others	4.7	5.0	
Insurance Types			
Private Insurance	49.3	54.6	0.15
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Self-pay	1.8	3.5	
Other	1.5	1.9	
Major reasons for this visit**			
New Problems	33.7	42.6	0.002
Chronic Problems	39.0	28.7	
Pre-/Post-Surgery	27.3	28.7	
Preventive Care	0.0	0.0	
Total Number of Chronic Diseases**	1.3	1.0	0.001

** statistical significant level at .05

Table 2. Practice Characteristics of Primary Care Physicians who Care for Patients with Rare Diseases using NAMCS, 2012-2014

	Patients with rare diseases	Patients without rare diseases	p-value
Practicing Area			
Urban	84.5	86.4	0.32
Rural	15.5	13.6	
Referral to Other Providers**			
Yes	14.3	9.0	0.01
No	85.7	91.0	
Time Spent with Providers (min)	22.4	21.3	0.09

** statistical significant level at .05

Table 3. Odds Ratios of Referral Using Unadjusted and Adjusted Logistic Regression Analyses using NAMCS, 2012-2014

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Not having a rare disease	Reference	Reference
Having a rare disease	1.69 (1.15-2.48)**	1.52 (1.01-2.28)**

*Controlled for age, gender, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established vs. new patient.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	n/a
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5-6
		(*e*) Describe any sensitivity analyses	

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	7-8, 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and Practice for Rare diseases in Primary Care

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Prevalence and Practice for Rare diseases in Primary Care

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Tables: 3

Keywords: Rare disease, primary care, scope of practice

Abstract

Objectives: There are more than 7,000 rare diseases in the US and they are prevalent in 8% of the population. Due to life-threatening risk and limited therapies, early detection and treatment are critical. The purpose of this study was to explore characteristics of visits for patients with rare diseases seen by primary care physicians (PCPs).

Design: The study used a cross sectional study using a national representative dataset, the National Ambulatory Medical Care Survey for the years 2012-2014.

Setting: Primary care setting

Participants: Visits to PCPs (n= 22,306 representing 354,507,772 office visits to PCPs).

Primary Outcome Measures: Prevalence of rare diseases in visits of PCPs was the primary outcome. Bivariate analyses and logistic regression analyses were used to compare patients with rare diseases and those without rare diseases and examined characteristics of PCP visits for rare diseases and practice pattern.

Results: Among outpatient visits to PCPs, rare diseases account for 1.6% of the visits. The majority of patients with rare diseases were established patients (93.0%) and almost half (49.0%) were enrolled in public insurance programs. The time spent in visits for rare diseases (22.4 minutes) and visits for more common diseases (21.3 minutes) was not significantly different (p=.09). In an adjusted model controlling for patient characteristics (age, sex, types of insurance, reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with

rare diseases were 52% more likely to be referred to another provider (OR 1.52, 95% CI, 1.01-2.28).

Conclusions: Visits for rare diseases are uncommon in primary care practice. Future research may help to explain whether this low level of management of rare diseases in primary care practice is consistent with a goal of a broad scope of care.

Strengths and limitations of this study

- This study is the first research to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.
- The study used population-based national representative data allowing for generalizability.
- Primary care physicians may play a vital role in providing continuous care and managing patients with rare diseases effectively.
- The study is limited to the actions recorded in one visit due to study design.
- The study was unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care

Introduction

Primary Care Physicians (PCPs) are trained to provide care for a broad scope of conditions within their patient population. When PCPs maintain a broad scope of practice this safeguards access and quality of care for the general population. Some of these conditions are managed directly by the PCP and with others the PCP coordinates the care for the patient. One recent study indicated that in one year, family physicians typically manage about 1,700 diagnoses in office visits, with 100 diagnoses managed frequently.(1)

In addition to common, high prevalence diseases like diabetes, hypertension and arthritis, a substantial proportion of the general patient population, has a rare disease, or diseases. As of 2017, the National Institute of Health (NIH) Genetic and Rare Disease Information Center (GARD) had identified 7,000 rare diseases, affecting approximately 25-30 million people in the US population. (2) Rare diseases are categorized as life-threatening, with only few limited effective therapies available. In addition to the emotional and physical burden associated with diagnosis, patients with a rare disease often face financial burden due to the significant cost associated with drugs and therapies. As such, early detection and treatment are critical. For example, in one study, more than half of patients with rare diseases being seen at a PCP practice had been diagnosed with rare diseases at a PCP practice.(3)

However, to date there have been few studies investigating the role of PCPs in the management of patients with rare diseases. The purpose of this study was to

examine in a nationally representative sample of visits, the prevalence of rare diseases cared for in primary care practice as well as characteristics of patients and providers.

Methods

This study used the National Ambulatory Medical Care Survey (NAMCS), a national representative dataset, for the years 2012-2014. The NAMCS is a national probability sample survey of ambulatory medical care visits to office-based physicians that allows for national estimates regarding medical care in the US. (3) Nonfederally employed physicians defined by the American Medical Association and the American Osteopathic Association who were principally engaged in patient care activities and who are not specialized in anesthesiology, pathology and radiology were eligible. Also physicians who are younger than 85 years of age at the time of the survey were eligible. Based on multistage probability design, eligible PCPs were selected and informed about the survey and those who agreed to participate to the survey were included in the data. (3) NAMCS data is collected annually by the National Center for Health Statistics (NCHS). It is electronic record collected by the Census Bureau in the US and multiple steps were implemented to process and review the data based on the NCHS protocol. The data estimates to be reliable met two criteria, 1) sample records should be at least 30, and 2) a relative standard error should be 30 percent or less. (3) The sample frame for NAMCS data in the years 2012-2014 was composed of PCPs who specialize in primary care (e.g., General and Family Practice, Internal medicine and Pediatrics), and who identified themselves as the primary care physician (PCP) of the patient.(4) This list conforms to the definition used by the NAMCS to categorize primary care. Diagnosis was determined based upon the ICD-9 codes and the diagnosis made by a PCP at a visit

was electronically recorded in the patient record form. The patient report form provided preexisting conditions, current diagnosis and new diagnosis. (5) Thus, more than 30 diagnoses can be managed via this report form. (6) Furthermore, this report form allows us to identify established patients who have visited before whereas it does not allow us to estimate numbers of previous visits. The unweighted sample size was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014.

Rare disease

A rare disease is defined as a disease or a disorder that affects fewer than 200,000 people in the US.(2, 7) For this study, diagnoses were identified as a rare disease using the list provided by the GARD Information Center.(2) Two independent researchers and (i.e., Dr. Jo and Larson) and one family medicine physician (i.e., Dr. Carek) reviewed all new diagnosis in designated study years and identified rare diseases by comparing the list of GARD. With consensus agreements, rare diseases for the study were determined.

Independent Variables

Demographics of patients seen by PCPs, such as age, gender and race/ethnicity, were used. Gender and race/ethnicity (i.e., Non-Hispanic White, Non-Hispanic Black, Hispanics and Others) were considered categorical variables whereas age was used as a continuous variable. In addition, their form of health insurance, major reason for the visit, and total number of diagnosed chronic diseases were included as categorical variables. Health insurance was stratified into four categories: private insurance, public insurance such as Medicaid and Medicare, self-pay, and others. Major reason for the

visit was also categorized into four groups: new problems, chronic problems, pre- or post-surgery care and preventive care.

Providers' characteristics including practice location (i.e., urban or rural), referral to other providers (i.e., yes or no) were examined. Time spent with providers in primary care setting was compared between patients with rare diseases and those without rare diseases. Time spent with providers in primary care is the length of the time the provider spent with the patient at the office and patient's waiting time to see the provider, receive care from providers and prepare for a patient such as reviewing medical chart or physical examination were excluded. (3)

Statistical Analysis

To account for the complex survey design used in the NAMCS, a weighted variable was used to consider survey design effect. This allows for us to provide national estimates of United States ambulatory health care visits to office-based physicians and community health centers.(3) Also, it allows us to produce national estimates of the ambulatory health care utilization in the US (3). The prevalence of rare disease seen in the primary care office visit was estimated. Chi-square tests were used to compare characteristics of PCPs who care for rare diseases against those who do not. Logistic regression was also employed to examine the association between PCP referral to other providers and patient diagnosis of a rare disease. All analyses were conducted in SAS version 9.4 (Cary, NC). This study was approved as exempt by the Institutional Review Board at the University of Florida.

Patient and Public Involvement

Patients and/or public were not involved in this study.

Results

The final sample was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014. A total of 1,508 PCPs participated to submit data for sample patient visits. Of the total patient visits to a PCP, a rare disease was noted in 1.6% of those visits. PCPs cared for 177 different rare diseases. Patients with rare diseases were significantly older than those without rare diseases (age difference = 8.3 years, p<.01), while no significant differences were found in the distribution of sex and race/ethnicity (Table 1). The majority of patients with rare diseases were established patients (93.0%), having been seen by the PCP more than one time, and almost half (49.3%) were enrolled in private insurance programs. Of the visits for patients diagnosed with a rare disease, 39.0% visited their PCPs with a comorbid chronic problem. In addition, they had a higher total number of chronic diseases compared to patients without rare diseases (Table 1).

Of visits by patients with rare disease, 14.3% were referred to other providers (Table 2). While PCPs spent slightly more time with their patients who had rare diseases (22.4 min), compared to patients without rare diseases (21.3 min), it was not significantly different (Table 2). The majority of visits for patients with rare diseases and more common diseases who were seen by PCPs were located in urban areas. PCPs practicing in rural areas (7.6%) were not significantly less likely than PCPs practicing in urban areas (16.8%; p=.06) to refer patients with rare diseases to another physician. In

a bivariate analysis, care for rare disease was also not associated with rurality (p=.32) (Table 2).

In an unadjusted regression model, patients with rare diseases were 69% more likely to be referred to other providers than those without rare diseases. After controlling for covariates, such as patients' characteristics (i.e., age, sex, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with rare diseases were 52% more likely to be referred to another provider than those without rare diseases (Table 3).

Discussion

This study found that few patients with a rare disease were identified as being managed in primary care practice. Patients with rare diseases in the primary care setting show significantly older and have more comorbidities compared to those without a rare disease diagnosis whereas patients with rare diseases are comparable to those without rare diseases in terms of sex distribution, race/ethnicity and types of health insurance. Not surprisingly, visits in primary care for patients diagnosed with rare diseases are more likely than patients without rare diseases to lead to referral to another provider. To our knowledge, this is the first study to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.

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Competing Interests Statement: Drs. Peterson and Peabody are employees of the American Board of Family Medicine. No other authors have no declaration of conflict of interests.

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Rural	15.5	13.6	
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Yes	14.3	9.0	0.01
No	85.7	91.0	
Time Spent with Providers (min)	22.4	21.3	0.09

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	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Not having a rare disease	Reference	Reference
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*Controlled for age, gender, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established vs. new patient.

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Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	n/a
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Bias	9	Describe any efforts to address potential sources of bias	n/a
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Results			**Page**
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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
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Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Prevalence and Practice for Rare diseases in Primary Care: a national cross-sectional study in the United States

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Prevalence and Practice for Rare diseases in Primary Care: a national cross-sectional study in the United States

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Keywords: Rare disease, primary care, scope of practice

Abstract

Objectives: There are more than 7,000 rare diseases in the US and they are prevalent in 8% of the population. Due to life-threatening risk and limited therapies, early detection and treatment are critical. The purpose of this study was to explore characteristics of visits for patients with rare diseases seen by primary care physicians (PCPs).

Design: The study used a cross sectional study using a national representative dataset, the National Ambulatory Medical Care Survey for the years 2012-2014.

Setting: Primary care setting

Participants: Visits to PCPs (n= 22,306 representing 354,507,772 office visits to PCPs).

Primary Outcome Measures: Prevalence of rare diseases in visits of PCPs was the primary outcome. Bivariate analyses and logistic regression analyses were used to compare patients with rare diseases and those without rare diseases and examined characteristics of PCP visits for rare diseases and practice pattern.

Results: Among outpatient visits to PCPs, rare diseases account for 1.6% of the visits. The majority of patients with rare diseases were established patients (93.0%) and almost half (49.0%) were enrolled in public insurance programs. The time spent in visits for rare diseases (22.4 minutes) and visits for more common diseases (21.3 minutes) was not significantly different (p=.09). In an adjusted model controlling for patient characteristics (age, sex, types of insurance, reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with

rare diseases were 52% more likely to be referred to another provider (OR 1.52, 95% CI, 1.01-2.28).

Conclusions: Visits for rare diseases are uncommon in primary care practice. Future research may help to explain whether this low level of management of rare diseases in primary care practice is consistent with a goal of a broad scope of care.

Strengths and limitations of this study

- This study is the first research to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.
- The study used population-based national representative data allowing for generalizability.
- Primary care physicians may play a vital role in providing continuous care and managing patients with rare diseases effectively.
- The study is limited to the actions recorded in one visit due to study design.
- The study was unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care

Introduction

Primary Care Physicians (PCPs) are trained to provide care for a broad scope of conditions within their patient population. When PCPs maintain a broad scope of practice this safeguards access and quality of care for the general population. Some of these conditions are managed directly by the PCP and with others the PCP coordinates the care for the patient. One recent study indicated that in one year, family physicians typically manage about 1,700 diagnoses in office visits, with 100 diagnoses managed frequently.(1)

In addition to common, high prevalence diseases like diabetes, hypertension and arthritis, a substantial proportion of the general patient population, has a rare disease, or diseases. As of 2017, the National Institute of Health (NIH) Genetic and Rare Disease Information Center (GARD) had identified 7,000 rare diseases, affecting approximately 25-30 million people in the US population. (2) Rare diseases are categorized as life-threatening, with only few limited effective therapies available. In addition to the emotional and physical burden associated with diagnosis, patients with a rare disease often face financial burden due to the significant cost associated with drugs and therapies. As such, early detection and treatment are critical. For example, in one study, more than half of patients with rare diseases being seen at a PCP practice had been diagnosed with rare diseases at a PCP practice.(3)

However, to date there have been few studies investigating the role of PCPs in the management of patients with rare diseases. The purpose of this study was to

examine in a nationally representative sample of visits, the prevalence of rare diseases cared for in primary care practice as well as characteristics of patients and providers.

Methods

This study used the National Ambulatory Medical Care Survey (NAMCS), a national representative dataset, for the years 2012-2014. The NAMCS is a national probability sample survey of ambulatory medical care visits to office-based physicians that allows for national estimates regarding medical care in the US. (3) Nonfederally employed physicians defined by the American Medical Association and the American Osteopathic Association who were principally engaged in patient care activities and who are not specialized in anesthesiology, pathology and radiology were eligible. Also physicians who are younger than 85 years of age at the time of the survey were eligible. Based on multistage probability design, eligible PCPs were selected and informed about the survey and those who agreed to participate to the survey were included in the data. (3) NAMCS data is collected annually by the National Center for Health Statistics (NCHS). It is electronic record collected by the Census Bureau in the US and multiple steps were implemented to process and review the data based on the NCHS protocol. The data estimates to be reliable met two criteria, 1) sample records should be at least 30, and 2) a relative standard error should be 30 percent or less. (3) The sample frame for NAMCS data in the years 2012-2014 was composed of PCPs who specialize in primary care (e.g., General and Family Practice, Internal medicine and Pediatrics), and who identified themselves as the primary care physician (PCP) of the patient.(4) This list conforms to the definition used by the NAMCS to categorize primary care. Diagnosis was determined based upon the ICD-9 codes and the diagnosis made by a PCP at a visit

was electronically recorded in the patient record form. The patient report form provided preexisting conditions, current diagnosis and new diagnosis. (5) Thus, more than 30 diagnoses can be managed via this report form. (6) Furthermore, this report form allows us to identify established patients who have visited before whereas it does not allow us to estimate numbers of previous visits. The unweighted sample size was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014.

Rare disease

A rare disease is defined as a disease or a disorder that affects fewer than 200,000 people in the US.(2, 7) For this study, diagnoses were identified as a rare disease using the list provided by the GARD Information Center.(2) Two independent researchers and (i.e., Dr. Jo and Larson) and one family medicine physician (i.e., Dr. Carek) reviewed all new diagnosis in designated study years and identified rare diseases by comparing the list of GARD. With consensus agreements, rare diseases for the study were determined.

Independent Variables

Demographics of patients seen by PCPs, such as age, gender and race/ethnicity, were used. Gender and race/ethnicity (i.e., Non-Hispanic White, Non-Hispanic Black, Hispanics and Others) were considered categorical variables whereas age was used as a continuous variable. In addition, their form of health insurance, major reason for the visit, and total number of diagnosed chronic diseases were included as categorical variables. Health insurance was stratified into four categories: private insurance, public insurance such as Medicaid and Medicare, self-pay, and others. Major reason for the

visit was also categorized into four groups: new problems, chronic problems, pre- or post-surgery care and preventive care.

Providers' characteristics including practice location (i.e., urban or rural), referral to other providers (i.e., yes or no) were examined. Time spent with providers in primary care setting was compared between patients with rare diseases and those without rare diseases. Time spent with providers in primary care is the length of the time the provider spent with the patient at the office and patient's waiting time to see the provider, receive care from providers and prepare for a patient such as reviewing medical chart or physical examination were excluded. (3)

Statistical Analysis

To account for the complex survey design used in the NAMCS, a weighted variable was used to consider survey design effect. This allows for us to provide national estimates of United States ambulatory health care visits to office-based physicians and community health centers.(3) Also, it allows us to produce national estimates of the ambulatory health care utilization in the US (3). The prevalence of rare disease seen in the primary care office visit was estimated. Chi-square tests were used to compare characteristics of PCPs who care for rare diseases against those who do not. Logistic regression was also employed to examine the association between PCP referral to other providers and patient diagnosis of a rare disease. All analyses were conducted in SAS version 9.4 (Cary, NC). This study was approved as exempt by the Institutional Review Board at the University of Florida.

Patient and Public Involvement

Patients and/or public were not involved in this study.

Results

The final sample was 22,306 representing 354,507,772 office visits to PCPs in the US from 2012-2014. A total of 1,508 PCPs participated to submit data for sample patient visits. Of the total patient visits to a PCP, a rare disease was noted in 1.6% of those visits. PCPs cared for 177 different rare diseases. Patients with rare diseases were significantly older than those without rare diseases (age difference = 8.3 years, p<.01), while no significant differences were found in the distribution of sex and race/ethnicity (Table 1). The majority of patients with rare diseases were established patients (93.0%), having been seen by the PCP more than one time, and almost half (49.3%) were enrolled in private insurance programs. Of the visits for patients diagnosed with a rare disease, 39.0% visited their PCPs with a comorbid chronic problem. In addition, they had a higher total number of chronic diseases compared to patients without rare diseases (Table 1).

Of visits by patients with rare disease, 14.3% were referred to other providers (Table 2). While PCPs spent slightly more time with their patients who had rare diseases (22.4 min), compared to patients without rare diseases (21.3 min), it was not significantly different (Table 2). The majority of visits for patients with rare diseases and more common diseases who were seen by PCPs were located in urban areas. PCPs practicing in rural areas (7.6%) were not significantly less likely than PCPs practicing in urban areas (16.8%; p=.06) to refer patients with rare diseases to another physician. In

a bivariate analysis, care for rare disease was also not associated with rurality (p=.32) (Table 2).

In an unadjusted regression model, patients with rare diseases were 69% more likely to be referred to other providers than those without rare diseases. After controlling for covariates, such as patients' characteristics (i.e., age, sex, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established or new patient), patients with rare diseases were 52% more likely to be referred to another provider than those without rare diseases (Table 3).

Discussion

This study found that few patients with a rare disease were identified as being managed in primary care practice. Patients with rare diseases in the primary care setting show significantly older and have more comorbidities compared to those without a rare disease diagnosis whereas patients with rare diseases are comparable to those without rare diseases in terms of sex distribution, race/ethnicity and types of health insurance. Not surprisingly, visits in primary care for patients diagnosed with rare diseases are more likely than patients without rare diseases to lead to referral to another provider. To our knowledge, this is the first study to investigate characteristics of patients with rare diseases seen in primary care practice and the association between physician referral and rare disease diagnosis.

Much of medical practice and the corresponding comfort in diagnosing and treating conditions is affected by the frequency of occurrence of the condition and pattern recognition. Rare diseases are by their very nature uncommon and thus PCPs may not

always feel comfortable with the nuances of treatment and potential complications for a disease that they encounter very infrequently. According to the National Academy of Medicine, since rare diseases tend to accompany multiple common conditions, it disrupts a clinician's ability to recognize clues of rare diseases.(8) In many of these cases PCPs need more than a consult from a specialist, especially when the primary care team does not have the specialized medical knowledge. Receiving all of their care from specialists may not be the best situation for the patient. Patients with rare diseases need to be managed in primary care or at least have shared care between primary care and specialists in complementary roles to provide a more effective management of these complex patients.

There are some limitations to this study. First, due to the design of the NAMCS we are limited to the actions recorded in that one visit. The design does allow us to have an understanding of the types of patients seen in primary care but it is not data on a cohort of patients. Thus, we do not know what sort of care may have transpired between the patient and the physician in previous visits. Also, it is not able to explore the linkage of multiple consultations with specialists pre- or post-visit to PCPs. Second, we are able to see if patients are referred in that one visit, we are unable to determine if that referral is for a consult or part of a shared care relationship between primary care and specialty care.

Conclusion

This study identified characteristics of patients with rare diseases who are seen in primary care practice and the delivery patterns of PCPs managing patients with rare

diseases. Findings from this study suggest that PCPs must possess a broad scope of practice in order to deliver comprehensive, high-quality care. A better understanding of the overall management of patients with rare diseases managed solely outside of primary care would help to improve the care for these patients.

Acknowledgements

Contributors:

Ara Jo, PhD led the entire research as the first and corresponding author from writing the manuscript, analyzing the data and interpretation.

Samantha Larson, MPH, analyzed the data and contributed to writing the manuscript.

Peter J. Carek, MD, MS contributed to writing the manuscript.

Michael R. Peabody, PhD, contributed to writing the manuscript.

Lars E. Peterson, MD, PhD, contributed to writing the manuscript.

Arch G. Mainous III, PhD, contributed to writing the manuscript and guided the direction of the study.

Competing Interests Statement: Drs. Peterson and Peabody are employees of the American Board of Family Medicine. No other authors have no declaration of conflict of interests.

Funding Statement: This work was supported by a grant from the American Board of Family Medicine Foundation.

Ethics approval: This study was approved as exempt by the Institutional Review Board at the University of Florida.

Data availability statement: Data are available through the National Ambulatory Medical Care Survey access from https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm.

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Table 1. Characteristics of Patients with Rare Diseases in Primary Care, NAMCS 2012-2014 (unweighted N= 22,306, weighted N= 354,507,772)

	Patients with rare diseases (%)	Patients without rare diseases (%)	p-value
Unweighted Sample Size	363	21,943	
Weighted Sample Size	5,581,791	348,925,981	
Mean Age (year-old) **	47.7	39.4	<0.001
Sex			
Female	56.4	53.8	0.44
Race			
Non-Hispanic White	75.0	70.6	0.54
Non-Hispanic Black	8.6	10.1	
Hispanics	11.7	14.3	
Others	4.7	5.0	
Insurance Types			
Private Insurance	49.3	54.6	0.15
Public Insurance	47.3	40.0	
Self-pay	1.8	3.5	
Other	1.5	1.9	
Major reasons for this visit**			
New Problems	33.7	42.6	0.002
Chronic Problems	39.0	28.7	
Pre-/Post-Surgery	27.3	28.7	
Preventive Care	0.0	0.0	
Total Number of Chronic Diseases**	1.3	1.0	0.001

** statistical significant level at .05

Table 2. Practice Characteristics of Primary Care Physicians who Care for Patients with Rare Diseases using NAMCS, 2012-2014

	Patients with rare diseases	Patients without rare diseases	p-value
Practicing Area			
Urban	84.5	86.4	0.32
Rural	15.5	13.6	
Referral to Other Providers**			
Yes	14.3	9.0	0.01
No	85.7	91.0	
Time Spent with Providers (min)	22.4	21.3	0.09

** statistical significant level at .05

Table 3. Odds Ratios of Referral Using Unadjusted and Adjusted Logistic Regression Analyses using NAMCS, 2012-2014

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Not having a rare disease	Reference	Reference
Having a rare disease	1.69 (1.15-2.48)**	1.52 (1.01-2.28)**

*Controlled for age, gender, race/ethnicity, types of insurance, major reason for this visit, total number of chronic disease, having a rare disease and established vs. new patient.

** statistical significant level at .05

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
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		(*e*) Describe any sensitivity analyses	

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